CONTINUED CANNABIS USE AND RISK OF RELAPSE IN PATIENTS WITH A FIRST EPISODE PSYCHOSIS

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STATEMENT OF PERSONAL CONTRIBUTION

This project comprises a follow up study of patients with psychosis that were part of previous research projects using face-to-face interviews. Ethical approval of the follow up study was granted by the Ethics Committee at the Institute of Psychiatry, Psychology and Neuroscience prior to the beginning of my PhD. I contributed to defining the battery of assessments used in the follow up assessments. I organised, coordinated and carried out follow up assessments of about 290 patients with psychosis (out of whom I included only those who had their first assessment close around their onset of their illness) and I was responsible for blood and saliva collections from consented participants. Reaching such a large number of follow up assessments would not have been possible without the help of other research workers, which I trained and supervised together with my supervisor Dr Sagnik Bhattacharyya. I carried out a substantial number of face-to-face interviews myself (n=117), screening the clinical records for a number of subjects (n=110) and I entered a proportion of the collected data onto the database (n=114). I was responsible for all aspects of data management, including monitoring and processing the data entry that was done by other researchers involved. Finally, in discussion with my supervisors, I planned and conducted all statistical analyses and wrote this thesis in its entirety, with the following exception: The published papers were both circulated amongst co-authors and underwent peer review prior to acceptance, leading to editing of manuscript and proposals for additional analyses.

PREFACE

This thesis is a "Thesis incorporating publications". This implies that certain sections or chapters will be taken from published journal articles which I am the first author of.

Publications relating to the work presented in this thesis: three chapters are entirely made up of amended versions of the following published papers, including:

1. Chapter 3 comprising **Paper 1** (Schoeler, Monk, et al., 2016) and **Paper 4** (Schoeler, Murray, & Bhattacharyya, 2016) (cf. Appendix I)
2. Chapter 4 comprising **Paper 2** (Schoeler, Petros, Di Forti, Klamerus, et al., 2016), cf. Appendix I (cf. Appendix I)
3. Chapter 5 comprising **Paper 3** (Schoeler, Petros, Di Forti, Pingault, et al., 2016), cf. Appendix I (cf. Appendix I)

Related publications completed during the course of this PhD: Chapter 2 includes sections from published (or currently under review) papers, including

1. **Paper 5** (Schoeler, Kambeitz, Behlke, Murray, & Bhattacharyya, 2016) (cf. Appendix I)
2. **Paper 6** (Schoeler & Bhattacharyya, 2013) (cf. Appendix I)
3. **Paper 7** (Schoeler, Theobald, et al., 2016) (cf. Appendix I)
4. **Paper 8** (Schoeler et al., under review) (cf. Appendix I)
5. **Paper 9** (Foglia, Schoeler, Klamerus, Morgan, & Bhattacharyya, 2017) (cf. Appendix I)

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AUD	Alcohol use disorder
BAI	Becks Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988)
BPRS	Brief Psychiatric Rating Scale (Nuechterlein et al., 2006)
B-VAS	Bowdle Visual Analog Scales (Bowdle et al., 1998)
CADSS	Clinician Administered Dissociative States Scale (Bremner et al., 1992)
CAPE	Community Assessment of Psychic Experiences-state (N. Stefanis et al., 2002)
CB_1/ CB_2	Cannabinoid receptor type 1/type 2
CBD	Cannabidiol
CEQ	Cannabis Experiences Questionnaire (Di Forti, Marconi, et al., 2015)
CGI	Clinical Global Impression (William Guy, 1976)
CIP	Cocaine-induced psychosis
CSDD	Cambridge Study in Delinquent Development (Farrington, 1995)
CUD	Cannabis Use Disorder
DA	Dopamine
DAI	Drug Attitude Inventory (Townsend, Floersch, & Findling, 2009)
Digit Span	Digit span task (Conklin, Curtis, Katsanis, & Iacono, 2000)
DSM	Diagnostic and Statistical Manual of Mental Disorders (APA, 2013)
DSST	Digit Symbol Substitution Test (Weschler, 1958)
DUP	Duration of untreated psychosis
eCB	Endocannabinoid system
eCBs	Endocannabinoids
EE	Expressed Emotions
EMA/ESM	Ecological Momentary Assessment / Experience Sampling Methodology
FAST	Functioning Assessment Short Test (Rosa et al., 2007)
FEP	First episode psychosis
FU	Follow up
GABA	Gamma-aminobutyric acid
GAF	Global Assessment of Functioning scale (Frances, Pincus, & First, 1994)
Go/no-go	The Go/-no-go task (Newman, Widom, & Nathan, 1985)
HR	Hazard ratio
HVLT	The Hopkins Verbal Learning Test (Brandt, Corwin, & Krafft, 1992)
ICD	International Statistical Classification of Diseases and Related Health Problems (WHO, 2004)
IGT	Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994)
IH	Inhaled
IRR	Incidence rate ratio
IV	Intravenous
LCS	Life Chart Schedule (WHO, 1992)
MINI	Mini-International Neuropsychiatric Interview (Sheehan et al., 1998)
MNAR	Missing not at random
N	Number of subjects
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified
O	Oral
OR	Odds ratio
PAS	Premorbid Adjustment Scale (Cannon-Spoor, Potkin, & Wyatt, 1982b)
PET	Positron emission tomography
PANSS	Positive and Negative Syndrome Scale (Kay, Flszbein, & Opfer, 1987)

POMS	Profile of Mood States (de Wit, Enggasser, & Richards, 2002)
PPHS	Psychiatric and Personal History Schedule (Janca, 1993)
RAVLT	Rey Auditory-Verbal Learning Test (Schmidt, 1996)
RCT	Randomized controlled trial
REM	Random effects model
RMSEA	Root mean-squared error of approximation
RR	Relative risk
SANS	Scale for the Assessment of Negative Symptoms (Andreasen, 1989a)
SAPS	Scale for the Assessment of Positive Symptoms (Andreasen, 1984b)
SC	Synthetic cannabis
SCL	Symptom Checklist 90 (Derogatis, 1996)
SEM	Structural equation modeling
SES	Socioeconomic status
SOFAS	Social Occupational Functioning Assessment Scale
SPE	Single psychotic episode
SPECT	Single photon emission tomography
ST	Stop Task (Logan, Schachar, & Tannock, 1997)
SUD	Substance use disorder
THC	Delta-9-tetrahydrocannabinol
THCV	Delta-9-tetrahydrocannabivain
TSR	Target Symptoms Ratings Scale (Barber, Neese, Coyne, Fultz, & Fonagy, 2002)
VAS	Visual Analogue Scale (Folstein & Luria, 1973)
VTA	Ventral tegmental areal
VVLT	Visual and Verbal Learning Task (Marieke Liem-Moolenaar et al., 2010)
WCST	Wisconsin card sorting test (Puente, 1985)
WLS	Robust weighted least squares
WMD	Weighted mean difference

ABSTRACT

Although cannabis use following a first episode of psychosis (FEP) has been linked to poor outcome such as relapse, current understanding is limited regarding the nature of this association. To shed light on the nature of this relationship, this thesis employed multiple methodological approaches: First, I pooled together data from previous studies in order to estimate the cross-sectional effects of continued and discontinued cannabis use following the onset of psychosis and risk of relapse, using a meta-analytic design (**Paper 1**). Second, I prospectively collected follow up data from a cohort of patients presenting with a first episode psychosis to psychiatric services in south London. **Paper 2** examined the magnitude of effect of continued cannabis use on risk of relapse and related outcomes by grouping patients into classes of different patterns of cannabis use following onset of psychosis. In **Paper 3**, longitudinal modelling was employed to further examine whether the link between continued cannabis use and risk of relapse persists when non-causal explanations for the association are taken into account (reverse causation, premorbid genetic confounding).

My findings indicate that that former regular users who stopped using cannabis after the onset had the most favourable illness course with regard to relapse. The most unfavourable course was present in those who continued to use high-potency cannabis in a high frequency manner. The results also suggest that this association reflects a dose-dependent association that is unlikely to be a result of reverse causation (e.g. self-medication) or genetic and environmental (e.g. other illicit drug use, medication non-adherence) confounding. These findings point to reductions in cannabis use as a crucial interventional target to reduce risk of relapse in patients with a first episode psychosis.

1 FIRST EPISODE PSYCHOSIS

1.1 INTRODUCTION

Psychotic disorders are severe mental disorders that involve disturbances in thought, senses and perceptions, emotions and behavior. A psychotic episode is characterized by the presence of positive symptoms, including hallucinations (e.g. seeing, hearing, feeling things that are not there), delusions (e.g. fixed false beliefs) and thought disorder (e.g. disordered speech/writing, cognitive disorganization). Furthermore, the classification of psychotic disorders depends on the duration of the experience of the symptoms, as well as the presence or absence of affective symptoms, which can be classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (WHO, 2004). Hence, the onset of the illness is usually defined as the first occurrence of delusions, hallucinations and/or formal thought disorders (Lenior, Dingemans, Schene, & Linszen, 2005). About 3% of the population is diagnosed with a psychotic disorder over the lifetime (Perälä et al., 2007) and a recent study by the World Health Organisation (WHO) reported that the lifetime prevalence of any psychotic experience among adults was about 6% (J. J. McGrath et al., 2015). Despite the dimensional approach that is currently used to classify psychotic disorders, as evident in the ICD-10 (WHO, 2004) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (APA, 2013), recent studies have reported that a substantial proportion (between 1%-31%) of individuals in the general population experience psychosis-like symptoms, implicating that the symptoms may lie on a continuum within normal experiences (Nuevo et al., 2010). However, not all individuals with subclinical psychotic symptoms develop a full-blown psychotic

disorder, e.g. in help-seeking high-risk individuals, only a proportion transition to psychosis in the first year (22%) and the second year (29%) following first presentation (Fusar-Poli et al., 2012). The symptoms of psychosis usually manifest in adulthood and a substantial proportion of patients (~ 19%) present with their first episode before the age of 18 (early onset psychosis) (Schimmelmann, Conus, Cotton, McGorry, & Lambert, 2007). Psychotic disorders constitute one of the highest disease burdens globally (Whiteford et al., 2013) and are one of the most costly disorders, representing about 9% of all economic costs of brain disorders in Europe (Olesen, Gustavsson, Svensson, Wittchen, & Jönsson, 2012).

There is now increasing interest in the early stages of psychosis, i.e. the early period following the first episode of psychosis, which is also regarded as the "critical period" that determines long-term outcome in psychosis (Birchwood, Todd, & Jackson, 1997). The critical period hypothesis proposes a natural rapid progression of symptomatic, psychosocial and cognitive decline in the early phases of the illness (including the period of untreated psychosis), specifically in the first two to three years of the disorder (Birchwood et al., 1997). This progression of decline stops or slows down following the critical period and the level of disability or functioning remains subsequently. For instance, some studies have reported that the course stabilises after 2-5 years of the onset (Carpenter & Strauss, 1991; Crumlish et al., 2009). Other evidence showed that the greatest change (improvements in positive symptoms) occurred in the 6 months following onset and no significant further improvement was present between the following assessment periods (6 months to 12 months, 12 months to 18 months, 18 months to 24 months) (Szymanski, Cannon, Gallacher, Erwin, & Gur, 1996). This is in line with a study that reported that the greatest improvement in positive symptoms occurred within 1 year following the onset although improvement afterwards was still

significant (Jean Addington, Leriger, & Addington, 2003). Similarly, in a meta-analysis it was reported that the prevalence of patients with poor outcome did not increase with the duration of the follow up (Menezes, Arenovich, & Zipursky, 2006), which is a further indication of the stability of the course following the initial early stage of the illness. Together, evidence in support of a stable illness course following the early phase of illness does not greatly harmonise with the view of schizophrenia as a progressively deteriorating illness (Lieberman, 1999). The importance of early intervention to improve outcome in this period is also supported by the finding that early stage clinical markers (time spent experiencing psychotic symptoms in 2 years following the onset) were the strongest predictors for long-term outcome (25 years following the onset), including levels of symptoms, disability and course of illness (G. Harrison et al., 2001), implicating that the "critical period" is a crucial determinant of the long-term trajectory of psychosis. Hence, this very early phase of illness (e.g. the first 1-2 years) reflects a particularly sensitive period. For instance, premorbid factors appeared to have stronger effect in terms of predicting outcome in the early phases rather than later phases of the illness (R. J. Drake, Haley, Akhtar, & Lewis, 2000), for which reason this early stage of psychosis is considered as a crucial illness stage for research aiming to develop prediction models for outcome in FEP (Ram, Bromet, Eaton, Pato, & Schwartz, 1992).

Follow up research in samples of FEP patients has the advantage that patients are homogeneous with respect to their illness and results may be considered as more generalizable than those from samples comprising more chronic patients - a group which is likely to be more heterogeneous with regard to illness stage (e.g. effect of institutionalizations, interaction with aging, disease processes, multiple antipsychotic drug treatments). Importantly, it has been stressed that longitudinal studies (as opposed to cross-sectional investigations) of patients with psychosis are crucial in order to better

understand the course of the illness and associated risk factors (Ram et al., 1992). In the following sections, I will therefore primarily focus on follow up studies in patients with a first episode psychosis, i.e. not reviewing much of the evidence that was conducted in patients that are at later stages and/or employed cross-sectional study designs.

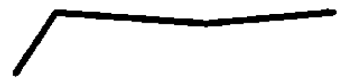
1.2 Outcome in first episode psychosis

1.2.1 Introduction

Earlier studies in FEP patients have typically defined outcome in terms of course patterns, in which outcome was defined as good outcome (e.g. about ~19% of patients exhibiting complete recovery without relapse) and poor outcome (~84% with one or more relapses or continuous illness course) (cf. *Table 1.* below). While those early studies on outcome in patients with psychosis suggest that for the majority of cases the course of the disorder is characterised by chronicity and deterioration (Hegarty, Baldessarini, Tohen, & Waternaux, 1993), recent studies are more in support of psychosis as an illness with a more favourable outcome than previously reported (Menezes et al., 2006). It has been pointed out that sample representativeness may have contributed to the high rates of reported poor outcome, e.g. earlier studies often included patients at different stages of their illness, which may have led to an over-representation of the more chronic, treatment-resistant patients (Menezes et al., 2006). Furthermore, outcome is heterogeneous and the reported rates for good/poor outcome vary depending on the definition of outcome. For instance, D. Addington et al. (2005) identified 44 different potentially useful measures that were used in previous studies when assessing outcome in FEP, out of which the most commonly employed outcome measures evaluating treatment efficacy included global functioning, symptomatic remission, relapse, positive symptoms, negative symptoms and depression. A recent meta-analysis that pooled together results from follow up studies in FEP reported that 42% of the samples were characterised by a "good outcome", which was defined by outcomes such as absence of relapse, achieved remission/recovery, improvement in scores from

symptom scales over time, being in employment, absence of committed/attempted suicide (Menezes et al., 2006).

Table 1. Patterns of course

Visual representation*	Description	n (%)[1]	n (%)[2]	n (%)[3]	Classification
	Complete recovery without relapse	11 (15%)	11 (22%)	8 (10%)	**Good outcome** 19% (mean) 10%-22% (range)
	One or more relapses, complete remissions	37 (51%)	17 (35%)	19 (24%)	**Poor outcome** 84% (mean) 78% -90% (range)
	One or more relapses, incomplete remissions	21 (28%)	4 (8%)	26 (33%)	
	Continuously psychotic	5 (6%)	17 (35%)	26 (33%)	

[1]Thara, Henrietta, Joseph, Rajkumar, and Eaton (1994) (10-year follow up)
[2]Shepherd, Watt, Falloon, and Smeeton (1989) (5-year follow up)
[3]N Goater et al. (1999) (5-year follow up)
*adapted from Thara et al. (1994)

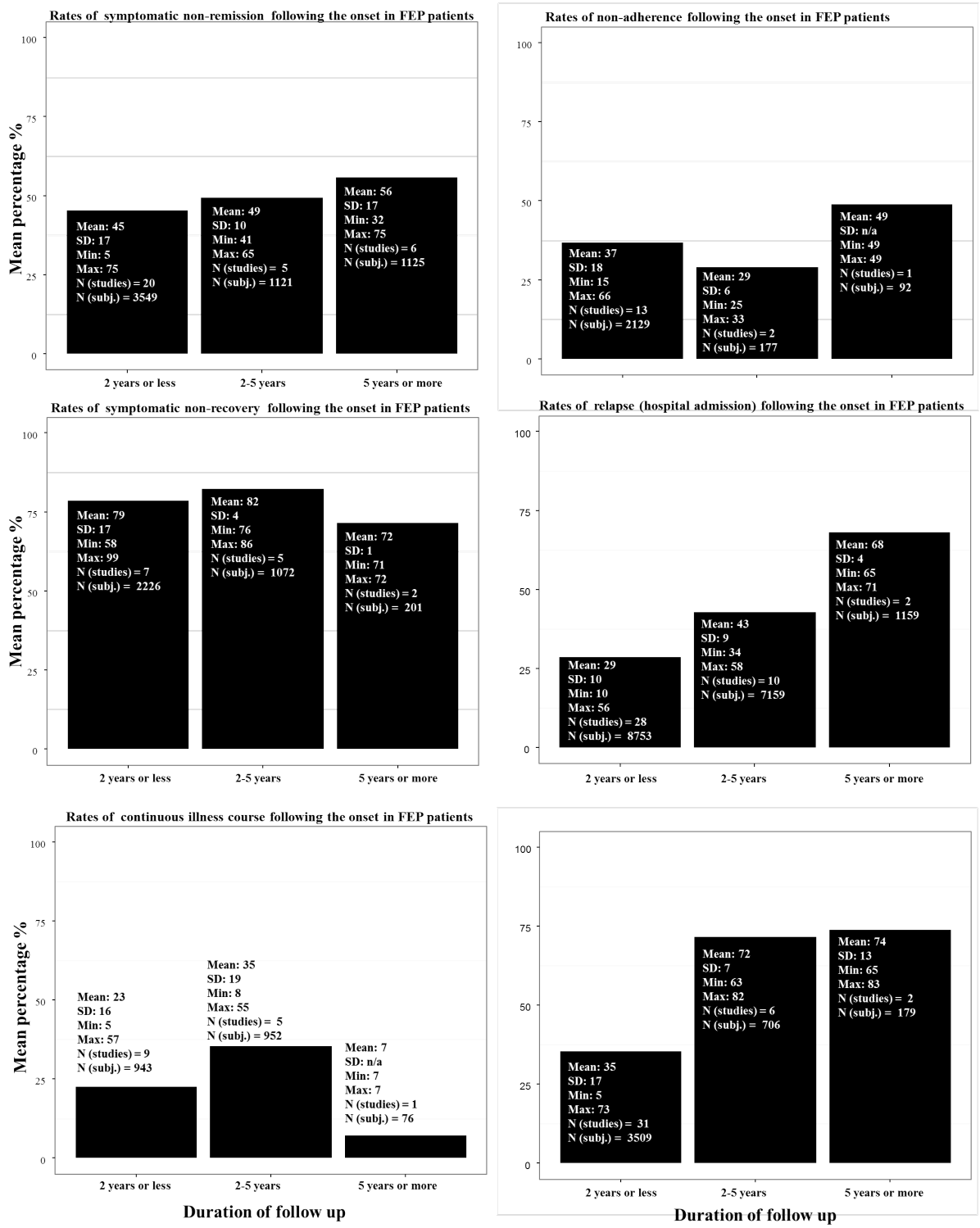
1.2.2 Clinical and functional outcome in first episode psychosis

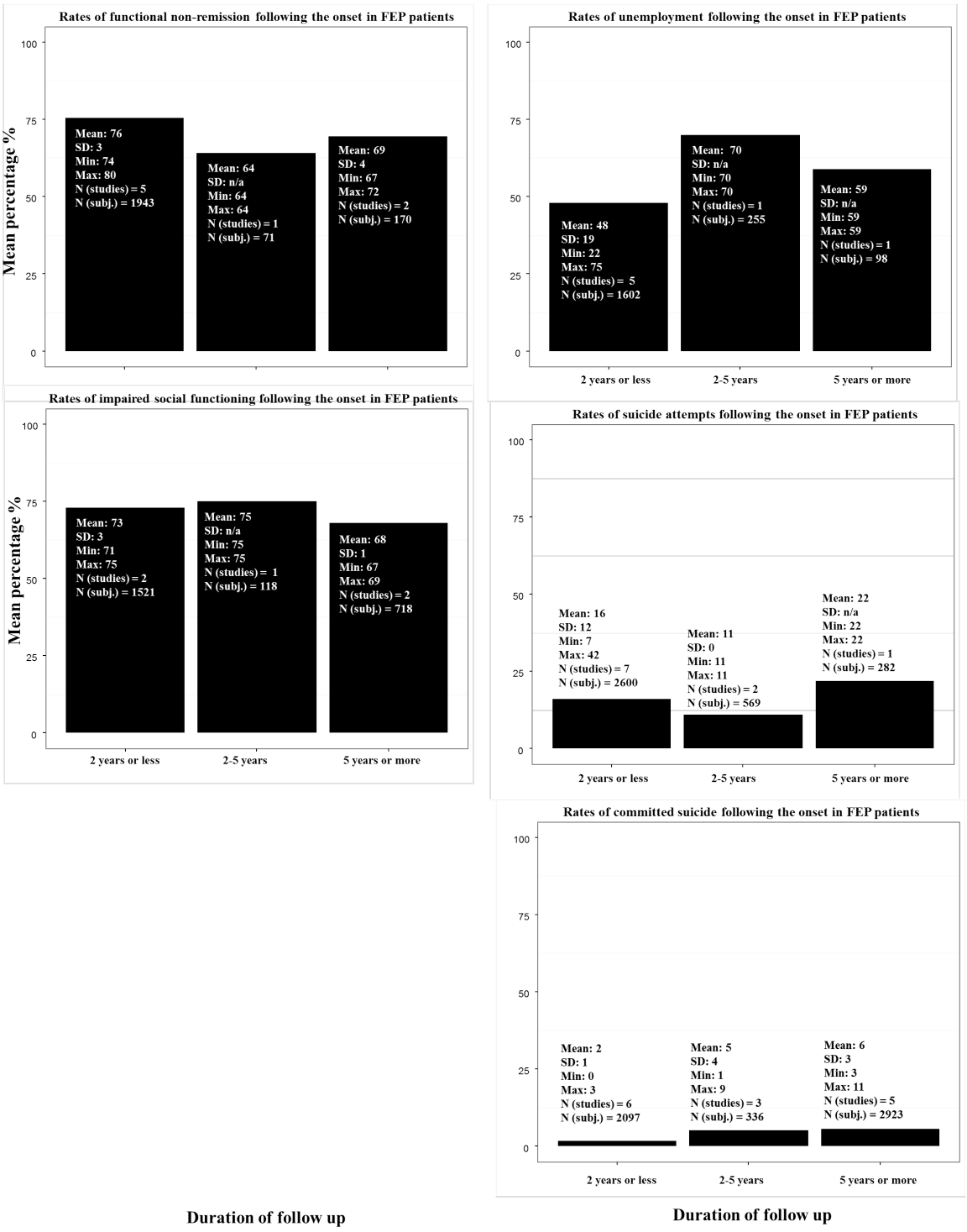
Illness course has been heterogeneously defined (Nuechterlein et al., 2006), and has often been studied by looking at (1) relapse or significant exacerbation of symptoms (episodic course, i.e. the experience of a relapse following the onset), (2) remission of illness (e.g. defined as absence of positive/negative/disorganized symptoms for a defined period of time), (3) recovery of illness [e.g. defined as absence of major symptoms including positive and negative, absence of psychosocial impairments, absence of relapses (Harrow, Grossman, Jobe, & Herbener, 2005)] or (4) continuous illness course (e.g. persisting symptoms following the onset, non-response to treatment).

As shown in *Figure 1.* below, the highest rates for "poor outcome" are reported when outcome is defined as non-recovery of psychosis, with studies reporting an average estimate of about 79% [range 58% - 99%] in the short-term (2 years of follow up or less), 82% [range 76% -86%] within the first 3 to 5 years of their illness and 72% in the long-term (more than 5 years following the onset). Those estimates also implicate that the prevalence rates of recovery in the early stage may not improve substantially following the first few years of the illness. Similarly, a meta-analysis in patients with established schizophrenia reported that only about 14% of patients would meet the criteria for recovery at follow up (Jääskeläinen et al., 2012). This study (Jääskeläinen et al., 2012) also reported that the rates of recovery were not significantly different in FEP patients when compared to non-FEP patients (17% vs. 11%) and that there was no significant increase in rates of recovery over the time of the illness course, supporting the view that there might be an initial early phase in which the rates raise and then stabilize. These rather pessimistic estimates of outcome may reflect the strict definition of recovery, since recovery is only achieved by those who meet the criteria for both symptomatic remission as well as functional remission (Chang et al., 2012; Verma, Subramaniam, Abdin, Poon, & Chong, 2012; Wunderink, Sytema, Nienhuis, & Wiersma, 2009). Considering that the rates for symptomatic recovery are usually much higher compared to functional recovery (77% vs. 29% at 6-months follow up) (Tohen et al., 2000) and only moderate overlap between functional and symptomatic remission (Verma et al., 2012; Wunderink et al., 2009), the low rates of recovery as reported by numerous studies seem plausible. In this context, it is important to distinguish between the different symptom dimensions, i.e. positive and negative symptomatology. For instance, whereas positive symptoms generally improve in most cases in response to antipsychotic medication (Jean Addington et al., 2003; Baeza et al., 2009; Goldberg et

al., 2007; González-Ortega et al., 2013; Hinton et al., 2007; Jahshan, Heaton, Golshan, & Cadenhead, 2010; Kopala et al., 2006; Leeson, Harrison, Ron, Barnes, & Joyce, 2012; Opjordsmoen et al., 2010; Prikryl et al., 2012; Renwick et al., 2015; Simonsen et al., 2007; Szymanski et al., 1996), the absence of changes in negative symptoms has often been reported (Baeza et al., 2009; Goldberg et al., 2007; González-Ortega et al., 2013; Hinton et al., 2007; Renwick et al., 2015; Szymanski et al., 1996), which reflects a major challenge in the treatment of FEP. Despite this apparent reduction in positive symptoms from onset to follow up, it seems also crucial to distinguish between different stages of the illness. For instance, in accordance with the critical period hypothesis, improvements in psychotic symptoms were present within 3 months following the onset, with only limited further improvements up to 1 year follow up (Simonsen et al., 2007). Similarly, the greatest improvement within 1 year following the onset in positive symptoms occurred within the first 6 months, although improvement afterwards was still significant (Jean Addington et al., 2003). Other evidence indicated that improvement in positive symptomatology occurred only in the first 6 months of the treatment in FEP patients and that no significant change occurred subsequently within the two years following the onset (Szymanski et al., 1996). Finally, it was reported that the degree of improvement in positive symptomatology was greater in the earlier (within 2 years following onset) than the later stages (5 years following onset) (González-Ortega et al., 2013) of illness. Finally, despite the symptomatic improvement, psychotic disorders are usually characterised by an episodic course, including high proportion of patients experiencing a relapse in the first two years following onset and/or non-remission of symptoms (cf. *Figure 1.*).

Figure 1. Clinical and functional outcome following onset of FEP





Note. Summary of prevalence rates reported by follow up studies in FEP patients (cf. *aTable 1.*, Appendix III)

Functional outcome has been assessed in different ways, including based on more objective criteria such as employment [e.g. functional recovery if in paid employment or enrolment in education (Fowler et al., 2009)] and/or in terms of change over time when assessed based on rating scales such as the GAF, SOFAS or PAS (cf. above, Table of abbreviations). A meta-analysis found that about 42% of FEP patients achieved functional recovery following the onset (Menezes et al., 2006). As shown in *Figure 1*., the majority (~60%-70%) of FEP patients did not achieve functional remission and remained impaired in their social functioning in both the early stages and the later stages of the illness. In accordance with the critical period hypothesis, functional improvement was found be greatest within the first 3 months following the onset and only little further improvements occurred up to the 1 year follow up (Simonsen et al., 2007). Similarly, it was reported that the degree of improvement was greater in the early stage of illness (2-year follow up) than in the later stages (5-year follow up) (González-Ortega et al., 2013). Assessing the trajectories of social disability, it was reported that the majority of FEP patients (66%) were characterised by high levels of disability at onset that did not improve over the 1-year follow up (Hodgekins et al., 2015). Level of function is also an important part of the concept of recovery in psychosis. For instance, while out of those who were classified as functionally remitted, 73% of those also met the criteria for recovery, while in those classified as symptomatically remitted the proportion of individuals that achieved recovery was much lower (37%) (Wunderink et al., 2009). Other evidence showed that, at a 2-year follow up, symptomatic remission was achieved by 54% and functional remission by 58%, while only a subset (29%) met the criteria for both symptomatic and functional remission (Verma et al., 2012). First, this may indicate that persistent functional disability can occur, even in the presence of symptom remission, but also that both

outcomes only partly overlap and, hence, somewhat different treatment approaches may need to be considered.

The costs of loss of productivity due to impairments in functioning such as unemployment or premature mortality have been estimated to be around 3.4 billion pounds (Mangalore & Knapp, 2007). As shown in *Figure 1.*, unemployment rates are on average around 50% or more in FEP patients throughout the different stages following the onset. A meta-analysis reported that about 39% of FEP patients were not in employment at follow up (Menezes et al., 2006). For instance, although a high proportion of unemployed patients at onset were in employment after 1 year of follow up (37%), there was a substantial proportion of patients that was in employment at the onset of illness and became unemployed throughout the follow up (23%) (J Addington, Young, & Addington, 2003).

The rates of completed suicides following onset are high and average prevalence rate range 2%-6% as found in follow up studies (cf. *Figure 1.*), which is similar to estimates reported by a meta-analysis (6%) (Palmer, Pankratz, & Bostwick, 2005). However, the rates of attempted suicides are higher (11%-22%) (cf. *Figure 1.*) and it has been reported that suicidal behaviour is particularly frequent in the early phase of the onset (Ayesa-Arriola et al., 2015; Mitter, Subramaniam, Abdin, Poon, & Verma, 2013; H Verdoux et al., 2001) or just before the onset of the illness (Ayesa-Arriola et al., 2015). Previous research indicate that several predictors may increase the risk for suicide, such as presence of depressive symptoms, male sex level of education, higher positive symptomatology, presence of manic symptoms, unemployment at onset and level of insight (Dutta, Murray, Allardyce, Jones, & Boydell, 2011; Geoffroy & Turecki; Sönmez, Romm, Andreasssen, Melle, & Røssberg, 2013). The high rates of suicidal behaviour also reflect the presence of depressive symptoms in FEP patient,

which frequently co-occur during the acute and early phases following the onset of psychosis (D. Addington, Addington, & Patten, 1998; González-Ortega et al., 2013; Sönmez et al., 2013) but also when assessed at later stages (e.g. 5-year follow up (Shepherd et al., 1989). Encouragingly, depression symptomatology usually improves following the onset to improve (González-Ortega et al., 2013; Shepherd et al., 1989) and only few cases develop depression following the onset (Sönmez et al., 2013). Nevertheless, it has been proposed that the issue of risk factors of suicide/depression deserves greater attention in this population, particularly the early phase, in order to develop better prevention strategies (Geoffroy & Turecki, 2016).

Other studies have investigated cognitive outcome in FEP patients. Cognitive deficits are considered as one of the core features of psychotic disorders (Kahn & Keefe, 2013). It has been suggested that neurocognitive function is an important dimension to be included in operational criteria for recovery (Wunderink et al., 2009) and it may also be considered as a correlate of functioning, given its association with the level of functioning in FEP patients (Allott, Liu, Proffitt, & Killackey, 2011; González-Ortega et al., 2013). Currently, there is fairly consistent evidence that cognitive deficits precede the onset of the illness. For instance, meta-analyses reported that cognitive impairments significantly predicted onset of psychosis, which was present in a dose-response fashion (Khandaker, Barnett, White, & Jones, 2011) and already present years prior to the onset (Dickson, Laurens, Cullen, & Hodgins, 2012). A recent meta-analysis investigating cognitive functioning in FEP patients reported medium to large deficits that were present in most domains of cognitive functioning when compared to healthy controls, especially in domains such as memory and verbal learning, executive functioning, attention and motor skills (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Looking at change over time in patients with

established schizophrenia, a meta-analysis found that cognitive function generally improves (most robustly in the domain of verbal and visual memory) or stays stable over time (Szöke et al., 2008), while progressive impairment is unlikely to occur. However, it needs to be considered that identified improvements may reflect a practice effect due to the repeated measures design. For instance, one study reported that the performance in many of the memory tests administered (9 out of 16) improved over time, but that this effect disappeared when controlling for practise effects (by control group of healthy controls) (Goldberg et al., 2007). Similarly, studies that followed up patients with a first episode psychosis mainly reported that there are no major changes over time in neurocognitive function in a 10-year follow up (Hoff, Svetina, Shields, Stewart, & DeLisi, 2005). In accordance, a recent systematic review in FEP patients concluded that cognitive function can be expected to remain stable following the onset (Bozikas & Andreou, 2011). Other evidence reported that FEP patients significantly improved in their neurological soft signs (NSS) over time (Prikryl et al., 2012). However, despite greater improvements in NSS in FEP patients when compared to healthy controls, patients assessed at follow up still exhibited greater impairments in NSS when compared to healthy subjects (Mayoral et al., 2012), indicating that achievement to a normal level of cognition present in the general population is unlikely to occur despite treatment. Nevertheless, although some studies have found that FEP patients performed worse in some cognitive domains at follow up (Albus et al., 2002; Jahshan et al., 2010), overall there is little evidence to suggest that cognitive function deteriorates following the onset, which is somewhat opposed to the theory of psychosis as a neurodegenerative disorder.

To summarize, several outcome measures have been employed when assessing "good" and "poor" outcome and the reported prevalence rates are likely to vary

depending on the specific outcome definition. Similarly, prediction models for the different outcomes are likely to yield more heterogeneous results due to the variety of outcome measures. Nevertheless, a recently published comprehensive review on predictors for outcome in FEP identified, several predictors have been identified that relatively consistently predicted outcome (clinical, functional, cognitive), including premorbid difficulties (premorbid adjustment, history of developmental disorder), longer duration of untreated psychosis (DUP), and greater baseline symptom severity (especially negative symptomatology) (Díaz-Caneja et al., 2015).

In the following section I will focus on the main outcome measure employed in my thesis – namely relapse of psychosis –, which is one of most commonly employed outcome measures in follow up studies in FEP patients and I will provide an overview of factors that have been investigated in the context of risk factors for relapse following the onset of psychosis.

1.3 Relapse in first episode psychosis

1.3.1 Definition

Relapse is defined as the recurrence of psychotic symptoms, which are of clinical significance and follow a period of partial or full remission of symptoms (J. F. M. Gleeson, M. Alvarez-Jimenez, S. M. Cotton, A. G. Parker, & S. Hetrick, 2010). This outcome (relapse as exacerbation of psychotic symptoms) is the most commonly used in epidemiological research in psychosis (Olivares, Sermon, Hemels, & Schreiner, 2013). When assessing relapse of psychosis, a range of different approaches have been employed. To illustrate, relapse definitions usually fall into one of the broader categories, such as relapse of symptoms requiring hospital admission, relapse of symptoms based on standardized rating scales, relapse of symptoms based on screenings from medical records or clinical judgement. Although numerous studies have assessed relapse using standardized and validated scales such as Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), Clinical Global Impression scale (CGI) (W Guy, 1976) or Brief Psychiatric Rating Scale (BPRS) (Nuechterlein et al., 2006), one problem that occurs is the apparent heterogeneity in the way relapse is operationalised, making comparisons across studies difficult (cf. below *Table 2.*). Similarly, in a recent review, it was outlined that studies have also lacked the use of standardized or validated observer measures for assessing relapse and that important aspects of it were not captured by how relapse was operationalized in many studies (J. F. Gleeson, M. Alvarez-Jimenez, S. M. Cotton, A. G. Parker, & S. Hetrick, 2010). In fact, the lack of a standardized measure for outcome such as relapse has been criticised in a recent review on outcome in FEP, since this variation in relapse definitions may have contributed to the inconsistencies in reporting across different studies (Díaz-Caneja et al., 2015).

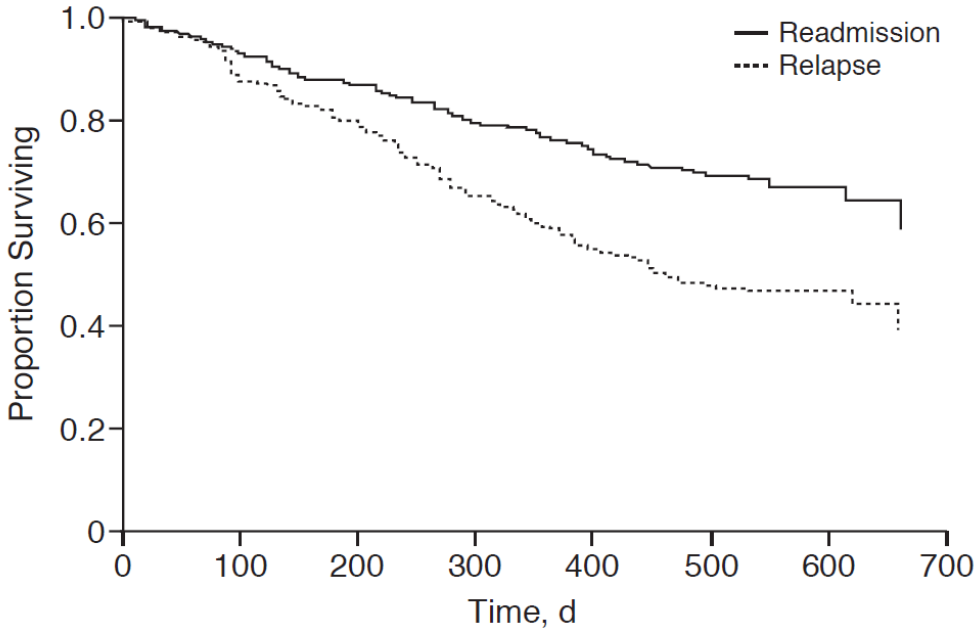
Table 2. Relapse definition based on rating scale

1	50% increase in the positive scale score (PANSS), sustained for at least 1 week (Gumley et al., 2003)
2	PANSS positive subscale score >13 (Chabungbam, Avasthi, & Sharan, 2007)
3	Increase in the CGI-overall severity score (Hong, Windmeijer, Novick, Haro, & Brown, 2009)
4	PANSS positive subscale score >4 (Bergé et al., 2016)
5	Rating of moderately/severe for at least 1 week PANSS positive or at least two on PANSS negative following a period of improvements (PANSS no greater than moderate) (Andreasen, Liu, Ziebell, Vora, & Ho, 2013)
6	Two-point increase and a score of six or seven on the TSR AND a score of six or seven on one of the key psychotic symptom items on the BPRS (Morken, Widen, & Grawe, 2008)
7	A rating of 6 or 7 on any of the BPRS psychotic items (Gitlin et al., 2001)
8	Having at least one BPRS psychotic item scored $\geq$ 5 or at least two BPRS psychotic items scored $\geq$ 4 (Girgis et al., 2011)
9	Increase in the PANSS > 10, CGI-Change score $\geq$ 6, and decrease in GAF score > 20 between 2 visits (Gaebel et al., 2010)
10	Relapse based on PPHS (emergence or exacerbation of positive, negative or disorganised symptoms following a period of remission of at least 30 days) (Turkington et al., 2009)
11	Increase in PANSS positive score >10 and a CGI- Change score > 6 and a decrease in GAF score >20 between two visits (Brinkmeyer et al., 2008)
12	(1) a rating of 6 or 7 on any items of the BPRS positive subscale for at least two weeks or (2) a rating of 5 plus a 2 point increase on one of the other two items (Üçok, Polat, Çakır, & Genç, 2006)
13	A score of 4 (moderate) or higher on PANSS following a period of 30 days without these psychotic symptoms (Holthausen et al., 2007)
14	A discrete period of symptomatology characterized by psychotic signs and symptoms of hallucinations, delusions, cognitive disorganization, marked psychomotor disturbance, and/or grossly inappropriate behaviour (based on LCS) (Alvarez-Jimenez et al., 2011)

Furthermore, there is only moderate overlap across different types of relapse definitions such as hospitalisation and those based on symptom rating scales, since only a subset of relapsing patients requires hospitalisation (Almond, Knapp, Francois, Toumi, & Brugha, 2004; Stefan Leucht et al., 2012). As shown in *Figure 2.*, estimates of relapse are higher when assessed with symptom scores and/or clinical judgement than those estimates that rely on hospitalisation data as indicated by different follow up studies [e.g. 29% for hospitalisation vs. 35% rating scale based at 2-year follow up, 43% vs. 72% at 5-year follow up, 68% vs. 74% at more than 5-year follow up, cf. *Figure 1*., above]. Similarly, out of all patients that were considered as relapsing based on rating scales (change in BPRS), only a subset was hospitalised as a result, with reported frequencies that range from 13% (Gitlin et al., 2001) to 35% (Üçok et al., 2006). This may illustrate that symptom scales also capture less severe episodes that do not require hospital admission and can be treated by community mental health services. Although relapse defined as admission to the psychiatric hospital may be regarded as a rather conservative measure that may not capture all visible exacerbations of psychotic symptoms, relapse definitions based on rating scales may result in too inclusive criteria, leading to over-estimation and non-comparability of the relapse rates reported (Suzuki et al., 2014). Furthermore, relapse as admission to the hospital following the onset of illness remains the most commonly employed operationalization (J. F. M. Gleeson et al., 2010). This operationalization has been suggested as a valid measure for relapse (D. E. Addington, McKenzie, & Wang, 2012) that is universally applicable (Burns, 2007) and captures high rates of relapse that are based on clinical judgement (D. E. Addington, Patten, McKenzie, & Addington, 2013; Almond et al., 2004). Although the threshold for requiring hospital admission may vary depending on the setting, it represents a concrete measure that can be assessed in most if not all health care systems,

is fairly robust and an intuitively interpretable outcome measure. For this reason, relapse defined as hospitalisation has been proposed as a valuable outcome measure in RCT's (Burns, 2007) that should be reported in all future RCT's to facilitate comparability (Stefan Leucht et al., 2012). This reflects its advantage of high face validity (i.e. clinicians have a sense of when patients should be admitted and what this would mean for the individual) and accessibility for economic analysis. It may be worth noting that the definition of relapse does not necessarily take into account those individuals who suffer from a continuous illness course. For instance, even if a patient is considered as non-relapsing, the person may still experience a continuous course of illness. However, majority of patients are characterised by a relapsing rather than continuous course of illness (cf. *Table 1.* above). To illustrate, when classified into different groups, a 5-year follow up reported that out of the whole sample 78% relapsed, 8% had a continuous course and only 14% did not belong to any of those groups (Andreasen et al., 2013). On the other hand, this also indicates that only a small proportion of patients experience a single psychotic episode (SPE = non-relapsing and non-continuous illness course). In another follow up study (7.5 years), the prevalence of SPE patients was estimated to be about 17% (Alvarez-Jimenez et al., 2011).

Figure 2. Proportion of FEP patients surviving without relapse/readmission during follow up



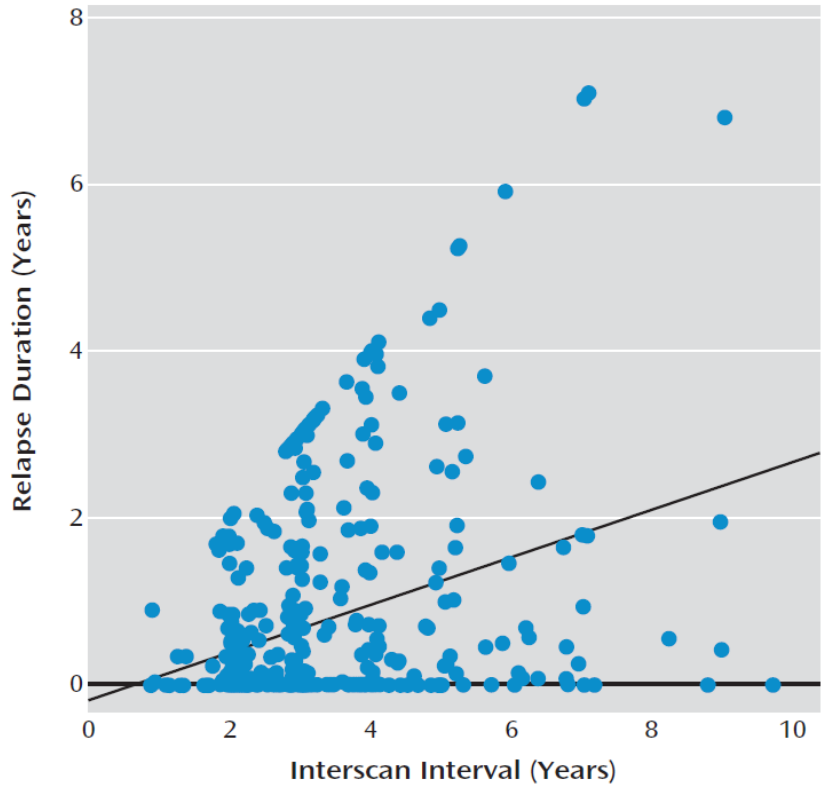
Note. Graph taken from R. J. Drake et al. (2007): Rates of readmission and relapse (exacerbation of positive symptoms lasting at least two weeks, leading to a change in management, including increase in medication and/or hospitalisation) in 18 months following the onset.

1.3.2 Relapse characteristics within the course of psychosis

Discouragingly, the occurrence of a relapse is common following the onset of psychosis, e.g. upto 50% of first episode psychosis patients experience a relapse that results in hospital admission within the first 2 years of illness, with the risk increasing to over 80% by the 8th year as reported by a recent meta-analysis (M Alvarez-Jimenez et al., 2012). Relapse rates are high in the early critical periods of the course of illness, with average rates of 29% (when defined as hospital admission) and 35% (when defined based on rating scales) within the first two years following onset (cf. *Figure 1*.above). In accordance with the critical period hypothesis (Birchwood et al., 1997), studies that assessed relapse rates in yearly intervals following onset reported that most relapses occurred within the first and second year in a 3-year follow up (D. Addington et al.,

2010) and 5-year follow ups (Patel R et al., 2016; Wiersma, Nienhuis, Slooff, & Giel, 1998). In this context, it has also been reported that the early phases of psychotic illness are characterised by multiple episodes of short duration, and whilst frequency of episodes decrease their duration lengthens as the illness progresses (Andreasen et al., 2013) (cf. below *Figure 3.*).

Figure 3. Plot of Duration of Relapse



Note. From Andreasen et al. (2013): Scatterplot depicts the pattern of symptomatic relapse in schizophrenia patients during the longitudinal follow-up period. Duration of relapse is plotted against each interscan interval (years). Early phases of the illness are characterized by multiple relapses of shorter durations.

Average time until a first rehospitalisation occurs is relatively short, which is estimated to occur on average about 5 months following the hospitalisation for the first episode (Üçok et al., 2006). Average length of time spent in a psychotic episode (based on PANSS) has been estimated to be about 8 months within the first 2 years following

onset of psychosis (Holthausen et al., 2007). Time spent in hospital following onset in a 5-year follow up was on average 6 months (Shepherd et al., 1989). Similarly, it has been reported that over the course of a 9-year follow up in FEP patients, they spend a substantial amount of this period in a relapse episode (14% of the time), even though the majority of this time was spent in remission (84% of the time) (Girgis et al., 2011). As shown in *Table 3.* (cf. below), not only do a high proportion of patients experience at least one relapse, but a substantial proportion of them is at risk to experience multiple relapses, including 2 (10% % - 36%), 3 (6% - 10%), 4 (4%-5%) and even more than 5 relapse (2%-22%) following onset.

Table 3. Prevalence rates for number of relapses following the onset

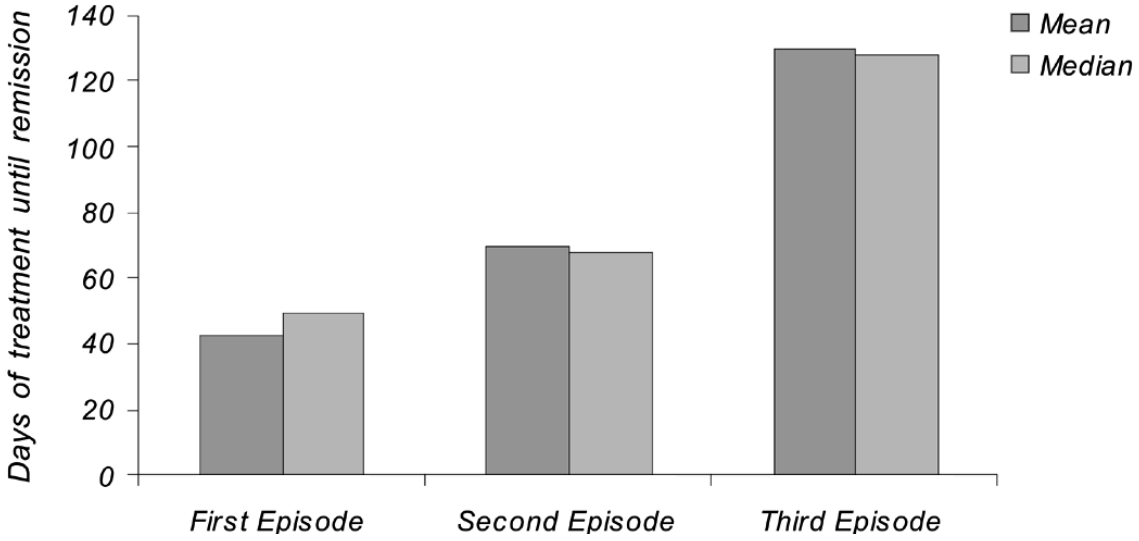
Study	FU	N	0 R	1 R	2 R	3 R	4 R	> 5 R
Chi et al. (2016)	10 Y	808	30%	20%	13%	10%	5%	22%
Thara et al. (1994)	10 Y	76	17%	39%	36%			2%
Eaton et al. (1992)	16 Y	1150	50%	19%	10%	6%	4%	11%
E. Y.-H. Chen et al. (2005)	3 Y	93	60%	27%	13%			
Shepherd et al. (1989)	5 Y	49	45%	29%	17%	9%		

Note. FU = Number of years (Y) of follow up; N = Number of subjects; R = Number of relapses during the follow up

There is also consistent evidence that those who experienced a relapse are at higher risk for a subsequent relapse (Ascher-Svanum et al., 2010; Carpenter & Strauss, 1991; Chabungbam et al., 2007; Doering et al., 1998; Heider, Kilian, Matschinger, Toumi, & Angermeyer, 2004; Kam, Singh, & Upthegrove, 2015; San, Bernardo, Gómez, & Peña, 2013a). To illustrate, D. Robinson et al. (1999) reported that about 82% of FEP patients experience a relapsed following the onset. In this first-relapse group, 78% had a second relapse and in the second-relapse group about 86% showed a third relapse. Another report found that the emergence of one relapse during the period of mental health care following the onset was predictive of further relapses following discharge from the services (Kam et al., 2015). As illustrated in *Figure 4*., it has been

reported that each additional relapse increase the duration of time until remission of the episode occurs. To illustrate, (Lieberman et al., 1995) reported that in FEP patients, the mean duration until remission following antipsychotic treatment was about 40 days, while this duration increased to a mean of about 60 days following the second episode and increased further (more than 120 days until remission) following the third episode. In accordance, it has also been reported that relapsing patients with established schizophrenia had a shorter time since the most recent relapse when compared to non-relapsing patients (Almond et al., 2004). Hence, patients with recurrent episodes are more likely to develop residual symptoms that only partially respond to the available treatment (Lieberman et al., 1998), again supporting the view that multiple relapses can be seen as a poor prognostic factor linked to disease progression to the worse. Number of relapse has also been linked to poorer cognitive functioning (Eberhard, Riley, & Levander, 2003), which is consistent with the observation that a relapsing course of illness (number of hospitalisations) is associated with loss of grey matter density in the frontal lobe (van Haren et al., 2007). Although a recent study failed to replicate the association between brain volume change and number of relapse, they found an association between duration of relapse and frontal lobe tissue loss that was independent of exposure to antipsychotic treatment (Andreasen et al., 2013).

Figure 4. Psychotic episodes and time to remission



Note. Duration of treatment until the achievement of remission of symptoms during the different episodes of psychosis [from Lieberman et al. (1995), modified by Müller (2004)]

1.3.3 Costs of relapse

The experience of a hospital admission due to a psychotic relapse is an event that has a significant impact on the lives of both patients and families. In terms of economic costs, hospitalisation is suggested to be one of the most costly treatments. For instance, it has significant implication for the utilisation of healthcare resources, with about 4 times the average estimated service costs in patients with psychosis that relapse, compared to those that do not (over a 6-month period) (Knapp, Locklear, & Järbrink, 2009a). Similarly, in other studies conducted in the UK that looked at relapse defined as re-emergence of psychotic symptoms in patients with established schizophrenia, it was suggested that service costs were about 2 to 4-times higher in in those who relapsed when compared to non-relapsing patients within a 6-months follow up period (Almond et al., 2004) or a 3-year follow up (Hong et al., 2009). In those studies, most of the cost difference was related to in-patient days (Almond et al., 2004) or to the event of hospitalisation (Hong et al., 2009). In the US, patients with established schizophrenia

who relapsed in a 6-months follow up were about 3-times more costly than those who did not (Atwood & Mackie, 2010). It has also been reported that the presence of psychosis (in comparison to absence of psychosis) in mentally ill patients admitted to the psychiatric hospital significantly increased the costs spent per patient (Curto, Masters, Girardi, Baldessarini, & Centorrino, 2016). Finally, relapsing FEP patients are more likely to be unemployed in the year following the onset than non-relapsing patients (Schennach et al., 2012; Üçok et al., 2006), for which reason this event results in indirect costs for society due to loss of productivity.

Despite the high economic costs associated with hospitalisation, there are some concerns that this outcome may not necessarily represent a patient-centered outcome (Burns, 2007). However, different lines of evidence implicate relapse as an event that crucially impacts on the patient's life and illness course. It has been consistently implicated as a maker for increased illness severity (D. E. Addington et al., 2012; Almond et al., 2004; Chabungbam et al., 2007), a chronic illness course (Köhler, Petersen, Benros, Mors, & Gasse, 2016) , lower quality of life (D. E. Addington et al., 2012; Almond et al., 2004; Pencer, Addington, & Addington, 2005) and lower level of functioning (Chabungbam et al., 2007; Kam et al., 2015; Üçok et al., 2006) in patients with psychosis. Furthermore, other evidence indicated that those who relapsed were more likely to be depressed (Atwood & Mackie, 2010), characterised by higher rates of suicide of suicidal ideation (Almond et al., 2004; Kazadi, Moosa, & Jeenah, 2008a) and higher number of suicide attempts (Togay, Noyan, Tasdelen, & Ucok, 2015). In terms of patient's experiences linked to the event of hospitalisation as a results of a relapse, it was reported that young people with a first episode perceive described this as a distressing, confusing and overwhelming experience (Fenton et al., 2014).

1.3.4 Predictors for relapse in first episode psychosis

A number of predictors have been identified to impact on risk of relapse following the onset, some of which are fixed (e.g. gender, mode of onset, age of onset etc.) and some of which are potentially modifiable following the presentation for the first episode of psychosis, i.e. amendable for intervention. The following section will therefore focus on both types of predictors (time-invariant vs. time-variant) in separation.

1.3.2.1 TIME-INVARIANT

Several predictors have been identified as predictors for relapse that reflect stable, i.e. unchangeable factors that are not amendable by treatment. Knowledge on this issue is important since it helps to identify individuals that may be at a particular risk for relapse, e.g. based on their onset and premorbid characteristics (e.g. premorbid adjustment, DUP when presenting with the first episode, age of onset of illness) or their biological profile (genetic code, gender, family history of mental illness, ethnicity). Overall, evidence with regard to onset demographics and risk of relapse is relatively inconsistent and studies implicate that onset characteristics are generally not very predictive with regard to relapse (Wiersma et al., 1998).

First, a recent meta-analysis further indicated that out of those time-invariant factors that are commonly assessed in studies, premorbid adjustment stood out as the most consistent predictor for relapse (M Alvarez-Jimenez et al., 2012). For instance, poor premorbid adjustment was significantly related to risk of relapse or earlier relapses in a 1-year follow up (Levy, Pawliuk, Joober, Abadi, & Malla, 2012; Üçok et al., 2006), a 5-year follow up (D. Robinson et al., 1999) and an 8-year follow up (Alvarez-Jimenez et al., 2011). To the contrary, in other studies this factor was not predictive of relapse in a 2-year follow up (A Malla et al., 2008) or a 3 year follow up (Caseiro et al., 2012) as well as length of relapses throughout a 5-year follow up period (Lenior et al., 2005).

Other evidence indicated that the effect of premorbid adjustment on symptomatic improvement following the onset of illness was stronger in the early than later stages of psychosis (R. Drake et al., 2016), which would be in accordance with the critical period hypothesis. It has also been reported that the effect depends on how relapse is defined, since there was an effect of premorbid adjustment on relapse if defined based on symptom rating scales but not if defined as change in medication due to worsening of symptoms (Levy et al., 2012).

Second, the impact of DUP has been investigated in studies evaluating prediction models for outcome in FEP patients. Some studies reported that a longer DUP predicted time until a rehospitalisation occurred (Üçok et al., 2006) as well as risk of relapse following the onset (Alvarez-Jimenez et al., 2011; Wiersma et al., 1998). Nevertheless, the results are also conflicting with regard to risk of hospitalisation (D. Addington et al., 2010; T. J. Craig et al., 2000; Tarricone et al., 2014) and relapse (defined based on rating scales) (Caseiro et al., 2012; Levy et al., 2012; Üçok et al., 2006). Similarly, other studies reported that DUP was not predictive of length of relapses throughout the follow up period (Lenior et al., 2005). Overall, DUP may to contribute to poorer outcome, at least in the early stages. For instance, when evidence was pooled together in a meta-analysis, the results suggested that DUP significantly predicted outcome 6-months and 1-year follow up, including symptomatology (general, negative, positive), remission-status, quality of life, functioning and depression/anxiety (Marshall et al., 2005). At 2-year follow up, DUP predicted positive symptomatology but was not linked to negative symptoms or functioning (Marshall et al., 2005). In accordance, recovery in the two years following the onset was predicted by DUP (Wunderink et al., 2009).

Other studies have looked at the effects of childhood trauma and risk of relapse, although there is no available evidence from follow up studies in FEP to date (Petros et al., in press). A recent review suggests that the accumulated evidence data is not consistent with regard to the effect of childhood trauma and its risk on relapse (Petros et al., in press), which may be related to methodological weaknesses comprised by those studies. Since there is good evidence attributing a contributing role to childhood trauma for the development of psychosis and persistence of symptomatology (Stowkowy et al., 2016; Trotta, Murray, & Fisher, 2015), further studies are therefore needed to clear the picture with regard to relapse.

Third, several other onset severity measures have been evaluated. For instance, some studies found that severity of baseline symptomatology (D. Addington et al., 2010; Alvarez-Jimenez et al., 2011; Möller et al., 2002; Üçok et al., 2006), lower level of functioning (D. Addington et al., 2010; Gearing et al., 2009; Üçok et al., 2006), poorer cognition at onset (Stirling et al., 2003) and longer duration of hospitalisation at onset (Hui et al., 2013) significantly predicted relapse. Although these results are not consistent considering that replications failed to link risk of relapse to onset marker of illness severity, including severity of positive symptoms at onset (Alvarez-Jimenez et al., 2011), longer duration of hospitalisation at onset as a predictor (Alvarez-Jimenez et al., 2011; Hui et al., 2013) and age of onset of psychosis (D. Addington et al., 2010; Alvarez-Jimenez et al., 2011; Caseiro et al., 2012; Chi et al., 2016; Levy et al., 2012; A Malla et al., 2008; Üçok et al., 2006), IQ (Levy et al., 2012) or cognitive performance at onset (Brinkmeyer et al., 2008; Holthausen et al., 2007).

When comparing the risk of relapse in those with a diagnosis of affective psychosis (e.g. psychotic depression, bipolar disorder) to those with non-affective psychosis (e.g. schizophrenia, schizoaffective disorder), studies mainly reported no

significant differences in risk for relapse following the onset (Bergé et al., 2016; Gearing et al., 2009; Levy et al., 2012; Tarricone et al., 2014). Other studies suggest that the risk of relapse may depend on the diagnosis. For instance, there is evidence that those with a diagnosis of schizophrenia are at higher risk for relapse (Hui et al., 2013) and longer durations of relapse (Lenior et al., 2005) when compared to other diagnosis of psychosis (Hui et al., 2013). Overall, a recent meta-analysis did not find an effect of diagnosis on risk of relapse (M Alvarez-Jimenez et al., 2012).

Some studies have looked at ethnicity but did not report a link to risk of relapse (D. Addington et al., 2010; N. Goater et al., 1999). However, in a sample of patients with established schizophrenia, it was reported that black ethnic minority was significantly linked to relapse (Almond et al., 2004). In this context, it might be important to consider immigration as a separate factor, since the classification based on ethnicity does not necessarily completely overlap with this. Problematically, the results are largely inconsistent in FEP patients, e.g. there is some evidence that reported a greater risk of relapse in those who migrated in an 8-year follow up (Alvarez-Jimenez et al., 2011) and evidence that migration status was not linked to the number of hospitalisations in a 2-year follow up (Abdel-Baki, Ouellet-Plamondon, Medrano, Nicole, & Rousseau, 2015).

So far there is no consistent evidence with regard to the effect of gender. For instance, while some studies reported an increased risk for women to relapse (Gearing et al., 2009; Parker & Hadzi-Pavlovic, 1995), the majority of studies did not report an effect of gender for risk of relapse (D. Addington et al., 2010; Chi et al., 2016; Levy et al., 2012; A Malla et al., 2008; Tarricone et al., 2014; Wiersma et al., 1998) or time until a relapse occurred (Lenior et al., 2005). Only one study published to date implicated male gender as a risk factor for relapse (Üçok et al., 2006).

Finally, the current evidence is not in support of an association between family history of (any) mental illness and risk of relapse in FEP patients (Alvarez-Jimenez et al., 2011; Caseiro et al., 2012; Gearing et al., 2009).

To summarise, the relationship between premorbid and onset clinical and social factors and risk of relapse is complicated and inconsistencies across studies are common. Nevertheless, the most frequently identified risk factors for relapse seem to more premorbid illness characteristics such as longer DUP or premorbid adjustment. This is in line with a recent review on outcome, in which it was reported that several predictors relatively consistently predicted outcome (clinical, functional, cognitive), including premorbid difficulties (premorbid adjustment, history of developmental disorder) longer DUP, and greater baseline symptom severity (especially negative symptomatology (Díaz-Caneja et al., 2015). Evidence with regard to other factors such as gender, diagnosis, family history of mental illness or ethnicity is less clear. Therefore, further research in larger samples of FEP patients that include multiple risk factors is warranted to draw conclusions more confidently.

1.3.2.2 TIME-VARIANT

The identification of treatment and environmental factors that have an effect on risk of relapse and are potentially amenable to change would inform public health policies and would aid to the development of novel therapies targeting these factors.

First, it is now well established that antipsychotic drug treatments is effective in reducing relapse rates in patients with psychosis (Stefan Leucht et al., 2003; Stefan

Leucht et al., 2012). Although latter meta-analysis revealed that new generation antipsychotics were more effective in preventing relapse when compared to the conventional antipsychotics, this finding may relate to differences in adherence between patients treated with the two types of antipsychotics (Stefan Leucht et al., 2003). Subsequent evidence in FEP samples is rather mixed, i.e. studies reported either a higher risk related to typical antipsychotic medication (Üçok et al., 2006) or did not report risk differences between patients taking atypical and patients taking typical antipsychotic medication (Gearing et al., 2009). Clozapine was identified as the most effective medication in preventing relapse in FEP patients (Tiihonen et al., 2011) and those with established psychosis (Haro et al., 2006). Interestingly, the effect of antipsychotic medication appears to be more effective in preventing relapse in the early stage of the illness (1 year following the onset) than at the later stage of the illness (Hogarty, 1993), which is in support of the critical period hypothesis. Furthermore, medication discontinuation has been linked to relapse (Hirsch et al., 1996; D. Robinson et al., 1999), which was also reported by a recent study that showed 1-year relapse rate of 79% in those who discontinued treatment one year following the onset versus 41% in those who continued treatment (E. Y. Chen et al., 2010). Other studies reported that a poor response to antipsychotic treatment (indexed by a high number of medications prescribed following the onset) significantly predicted relapse in FEP (Gearing et al., 2009; Patel R et al., 2016). Despite the established effect of the maintenance/non-maintenance, prescription/non-prescription and response/non-response to antipsychotic medication in predicting relapse, many studies have linked medication non-adherence to relapse (Barbeito et al., 2013; Caseiro et al., 2012; Coldham, Addington, & Addington, 2002; Gearing et al., 2009; Michele Hill et al., 2010; Hui et al., 2013; Martin Lambert et al., 2010; Levy et al., 2012; Morken et al., 2008; Üçok et al., 2006; H Verdoux et al.,

2000) and involuntary readmission (H Verdoux et al., 2000) and there are only few studies that are not in support of this (Favre, Huguelet, Vogel, & Gonzalez, 1997; A Malla et al., 2008; Parker & Hadzi-Pavlovic, 1995). In fact, medication non-adherence has been reported to be the strongest predictor for relapse in multifactorial prediction models (Caseiro et al., 2012). Other relapse-related outcomes that were also found to be linked to medication non-adherence included days spent in hospital, number of hospitalisations and days under section (Morken et al., 2008). As a matter of fact, medication non-adherence therefore reflects a major problem in clinical practise, since the proportion of patient that become non-adherent following the onset is substantial (cf. *Figure 1.,* e.g. 37% non-adherence in patients followed up within the first 2 year of the illness, 29% in those followed up between 2 to 5 years and about 49% in those followed up for more than 5 years). Estimates from systematic reviews indicate that an average of 26% of patients with psychosis are not adherent (Nose, Barbui, & Tansella, 2003), although a recent review concluded that rates vary greatly (reported rates between 47% and 95%) across studies (Sendt, Tracy, & Bhattacharyya, 2015). To illustrate, more than 60% of FEP patients had at least one or more gaps in their antipsychotic medication use in one year following the discharge for their first episode (Mojtabai et al., 2002). Despite the strong effects of medication non-adherence, relapse rates in fully adherence FEP patients are still relatively high within the first year (about 22%) (Levy et al., 2012) or in the three year following the onset (about 36%) (E. Y.-H. Chen et al., 2005), indicating that non-adherence alone cannot fully explain the risk of relapse in medicated patients. In this context, another factor usually linked to medication adherence is insight into the illness (Lacro, Dunn, Dolder, Leckband, & Jeste, 2002). This has been found to increase the risk of relapse (Bergé et al., 2016; R. J. Drake et al., 2007), although not in all studies are in support of the link between relapse and insight (Caseiro et al., 2012) or

attitude towards medication and relapse (R. J. Drake et al., 2007). Overall, it can be summed up that medical treatment is a crucial determinant for outcome defined as relapse of psychosis, and several factors may modulate its effects, such as the prescribed type, timing of discontinuation, treatment response, a patient's adherence and the stage of illness when the treatments is started.

Second, psychosocial factors have been suggested to impact on the risk of relapse in FEP patients. With regard to the family environment, those exposed to high Expressed Emotions (EE) were more likely to relapse (Barrelet, Ferrero, Szigethy, Giddey, & Pellizzer, 1990), which is consistent with what has been found in samples of patients with established schizophrenia (Butzlaff & Hooley, 1998b). This is also in line with evidence that showed that psychoeducational family interventions were able to reduce rehospitalisation rates in schizophrenia (non-FEP) by reducing family burden, changing EE behavior from high to low, improving compliance, quality of life and social adjustment (Pitschel-Walz, Leucht, Bäuml, Kissling, & Engel, 2004). However, it has also been reported that parental expressed EE did not predict lengths of relapse in a 5-year follow up (Lenior et al., 2005). Another study reported that number of rehospitalisation was significantly predicted by the level of social support, independent from potential confounders such as DUP, premorbid adjustment and ago of onset (Norman et al., 2005). Similarly, those FEP patients that experienced a decrease in their level of social support following the onset were at higher risk for relapse compared to those who didn't (Gearing et al., 2009). However, in this context it appears difficult to disentangle as to whether the increased risk actually reflects a lack of social support per se or whether those who are characterized by a more severe illness course (i.e. relapsing course) are less socially skilled and therefore appear to have lower levels of social support. Considering the relationship between exposure to adult life events and the

subsequent development of FEP (Beards et al., 2013), other lines of evidence have looked at life events as a potential risk factor relapse, indicating that recent life-stress was a significant predictor for relapse in patients with established schizophrenia (Hirsch et al., 1996; Hultman, Wieselgren, & Öhman, 1997; AK Malla, Cortese, Shaw, & Ginsberg, 1990). In accordance with the critical period hypothesis, it was found that number of life events prior to rehospitalisation were more a contributing factor in the early stages of the illness (less than 3 episodes) than at a later stage (more than 3 episodes) (Castine, Meador-Woodruff, & Dalack, 1998).

Third, an important factor that has relatively consistently been linked to relapse is substance use following the onset of the illness. The most commonly abused substances in patients with psychosis include legal substance as alcohol and cigarettes or illicit drugs such as cannabis, stimulants and opioids (Cooper et al., 2012; Kivimies et al., 2016; Van Mastrigt, Addington, & Addington, 2004). Studies looking at the effects of substance use in FEP have applied different parameters, i.e. they may classified user into those with any substance use (including legal and illegal), they distinguished between legal and illegal drugs of abuse, or they investigated the effect of specific drugs separately. The main problem inherent to this approach is that there is usually a high overlap across the substances that are used (Arndt, Tyrrell, Flaum, & Andreasen, 1992), e.g. there is a substantial proportion of SUD patients diagnosed polysubstance abuse (A Malla et al., 2008), for which reason it is often difficult to identify groups of patients that can be classified as users of “cannabis only” , “cigarettes only” or “alcohol only”. For instance, investigating the effect of lifetime SUD as a predictor for relapse may not lead to valid conclusions regarding the questions as to (1) whether it is a specific substance in separation or the combination of multiple substances that may have harmful effects and (2) whether one substance is more

harmful than the other (Kivimies et al., 2016). The other challenge when investigating this issue is the change in pattern of use over time that needs to be taken into consideration. For instance, substance use is not a stable lifestyle characteristic, since it has been shown that substance use is often reduced following the onset of psychosis (M Lambert et al., 2005; Turkington et al., 2009). With regard to the effect on outcome, follow up studies reported that cessation of substance use significantly reduced the risk of relapse (Turkington et al., 2009) and increased the chance of achieving remission (M Lambert et al., 2005). Other studies are in further support of the association between post-onset substance use and increased risk of relapse (A Malla et al., 2008), which was also present in form of a dose-response relationship (D Wade et al., 2006). Although some studies are not in support of substance abuse predicting relapse (here defined as change in medication due to worsening of symptoms) (Levy et al., 2012), latter study found an effect of SUD on outcome when relapse was defined based on changes in symptom scales (Levy et al., 2012), while controlling for medication-adherence. Similarly, a recent meta-analysis reported that substance use discontinuation was linked to reduced positive symptom severity, lower levels of depression and better functioning, although there was no significant association with number of hospitalisations (Mullin et al., 2012a). However, this may reflect the methodological issue of including patients that are at different stages of their illness rather than a clean FEP sample. In an FEP sample, D Wade et al. (2006) reported an increased risk for inpatient admission for substance abusers, which was present for a subgroup of cannabis users and stimulant users but not those with AUD. Only limited evidence exists with regarding cigarette use and risk of relapse, a substance that came into focus only recently since studies noticed and increased risk for the development of psychosis and earlier onset of psychosis in heavy smokers (Gurillo, Jauhar, Murray, & MacCabe, 2015). Although one studies

reported that ongoing cigarette use but not former cigarette use was linked to an increased risk of relapse (Hui et al., 2013), this effect was not controlled for other substance use or cannabis use, which is problematic since cigarette use is closely related to substance abuse (Myers & Kelly, 2006). Nevertheless, this sample (Hui et al., 2013) was recruited from a catchment area in which substance abuse is less common than in the Western culture (e.g. only 3% of patients reported to use other substances), i.e. the effect is unlikely to be confounded by the use of other substances. Overall, while substance abuse is likely to affect outcome negatively and increases the risk for relapse, further studies should be conducted to investigate the substances abused in separation. Interestingly, there is some evidence that suggests that those patients with comorbid substance use are characterised by a better premorbid adjustment (Arndt et al., 1992) and may present with less severe negative symptomatology at onset (Jean Addington & Addington, 1998; Green et al., 2004). To put this in context, it has been proposed that substance abusing patients may represent a neurodevelopmentally less impaired subgroup of patients (Schoeler, Kambeitz, Behlke, Murray, & Bhattacharyya, 2015) (see **Chapter 2.5** for a more detailed discussion).

To summarise, while those identified factors are non-fixed (i.e. time-invariant), it should be pointed out that certain factors may be more easily amendable for intervention, including substance use or medication adherence. While robust evidence exists regarding the beneficial effects of medication adherence in preventing relapse, less is known regarding the longitudinal effects of the use and abuse of different substances following the onset and causality in this context has yet to be established. Other potential risk factors are not easily directly treatable (e.g. stressful life events). In those cases, intervention may try to elucidate mechanisms of actions that mediate those relationships such as the strengthening of coping mechanism to deal with stress or the

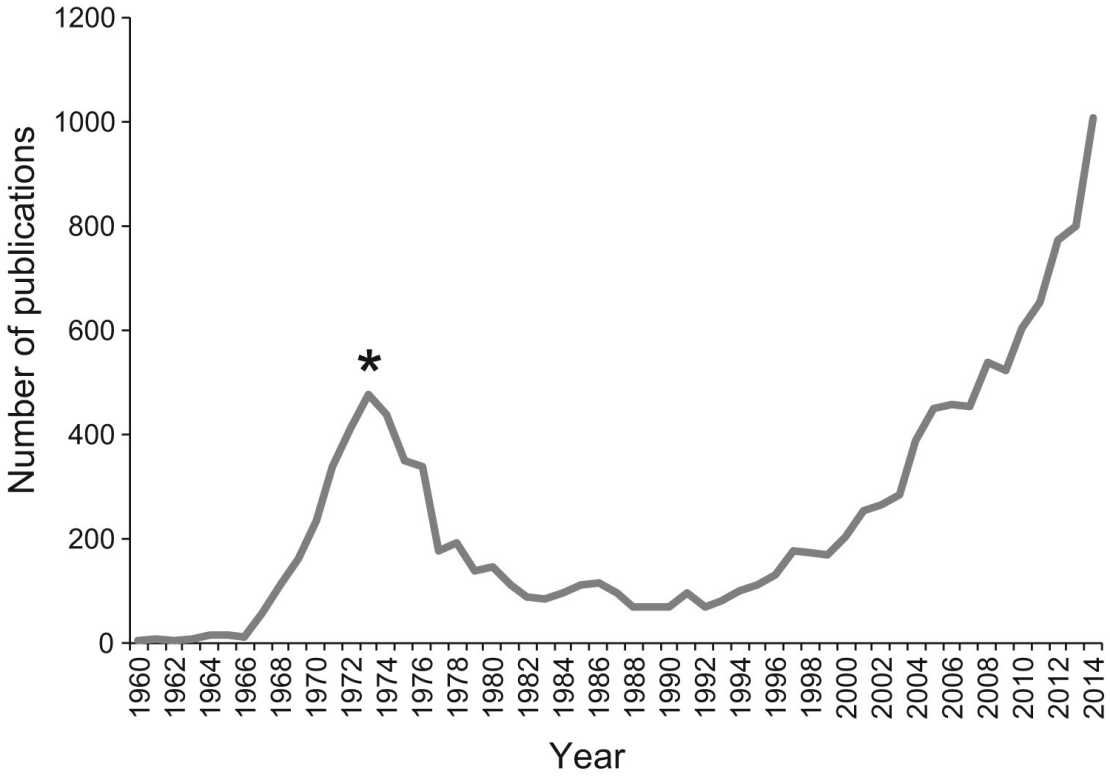
prescription of anxiolytic drugs. Identifying modifiable factors that impact on the course of the illness is therefore crucial in order to further provide evidence based specialized early intervention services.

2 COMPLEXITIES IN THE CANNABIS STORY

2.1 INTRODUCTION

The term cannabis refers to the different types of preparations derived from the plant *Cannabis Sativa*. Although the substance is known for its medical and textile use since ancient times (Russo et al., 2008), the recreational use of cannabis or use for medical purposes was rather uncommon until the 16th century but became more popular through medical prescribing or self-medication in the 19th and 20th century. There are now marked shifts in public attitudes to cannabis use and its legal standing in society in many countries (Benac & Caldwell, 2013; Reuter, 2010), making it to one of the most controversial topics debated by the public, policy makers and within the academic environment. In response to this, there has been a drastic increase in studies investigating the effects of cannabis (cf. *Figure 5*.), with about 13% investigating its neurobiological effects and approximately 27% aiming to elucidate its effects on behavioural outcome (Szutorisz & Hurd, 2016).

Figure 5. Cannabis research: Number of publications over time



Note. Taken from Szutorisz and Hurd (2016): Increase in research studies over recent decades that coincides with changes in the legalization status (~1996) and debates of recreational and medical marijuana use.
* The drop in publications in the 1970s marks changes in state laws and local regulations banning possession or sale of cannabis and cannabis becoming a schedule I drug in the US

The substance has now been recognized for both its toxic and therapeutic properties (Robin M Murray, Morrison, Henquet, & Di Forti, 2007). On the one hand there is evidence for its therapeutic effects for a range of pathological conditions such as cancer, neuropathic pain, movement disorders such as Parkinson's and Huntington's disease, multiples sclerosis, appetite stimulation and mood and anxiety disorders (Kumar, Chambers, & Pertwee, 2001; Whiting et al., 2015). On the other hand, there is now robust empirical ground to suggest that cannabis use may increase the risk for the development of psychiatric disorders, such as onset of psychosis (Di Forti, Vassos, Lynskey, Craig, & Murray, 2015; David M Fergusson, Horwood, & Ridder, 2005) and

its relapse (Patel R et al., 2016; Schoeler, Monk, et al., 2016; Schoeler, Petros, Di Forti, Klamerus, et al., 2016). Research on potential harmful and beneficial effects is crucial and has major public-health implications considering that cannabis remains the most commonly reported drug of dependence in the world after tobacco and alcohol (UNODC, 2014). The United Nations Office of Drugs and Crime (UNODC) reported a 12-month prevalence rate of cannabis use of 4% in the global populations aged between 15 to 64, corresponding to a total number of about 180 million of cannabis users worldwide (UNODC, 2014). In the EU, about 6% of the population (age 15-64) used cannabis within one year and the rates are particularly high (12%) in young adults (age 15-64) (EMCDDA, 2015) – e.g. the peak of the prevalence of cannabis use has been reported to be between the ages 20 and 24. The prevalence of cannabis use has increased in the last 10 years (Hasin et al., 2015), especially among young users (under 18) there was an 18-fold increase in prevalence (Hickman, Vickerman, Macleod, Kirkbride, & Jones, 2007). Cannabis use disorders (CUD) are defined as a set of consequences related to the drug use that can include impaired control, social/interpersonal problems, risky and hazardous use, legal problems and pharmacological effects such as tolerance, withdrawal or craving (APA, 2013). The 12-months prevalence rate of CUD is estimated to range between 2% and 5% globally (Hasin et al., 2015; UNODC, 2014). Given the increases in rates of cannabis use in the general population, the gathering of knowledge regarding its potential health risks is therefore of major interest for policy makers, especially in light of the current political debates regarding the legal health status of cannabis (Temple, 2015).

2.2 CANNABIS AND THE ENDOCANNABINOID SYSTEM

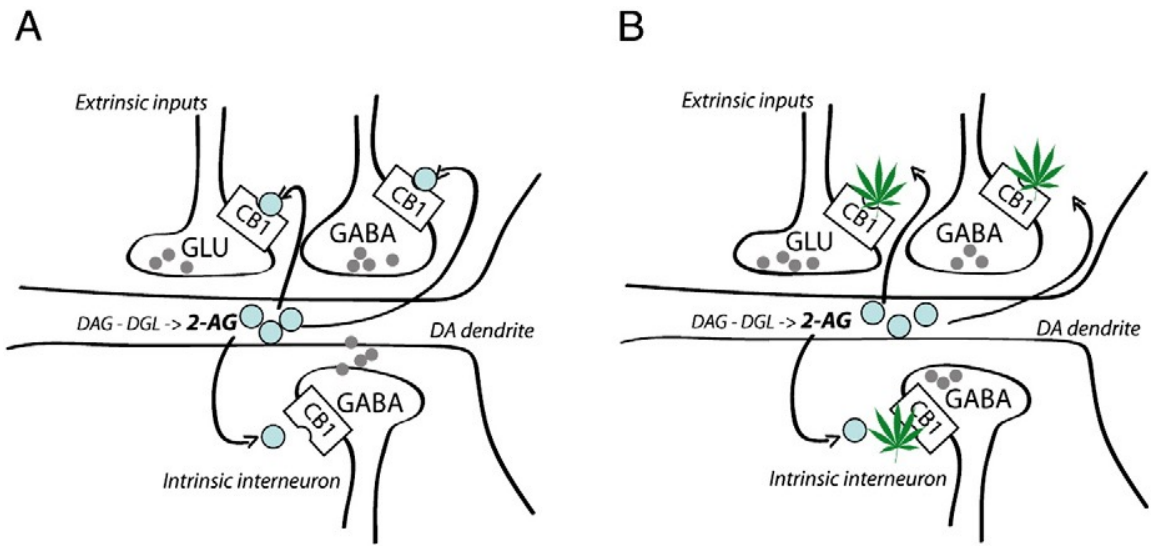
For the research community, a major milestone was the isolation of delta-9-tetrahydrocannabinol (THC) in the 1960th by chemist Raphael Mechoulam (Mechoulam & Hanuš, 2000), which contributed to the growing interest into the plants pharmacology and epidemiology. This was followed by the discovery of two new receptors in the brain, namely the CB_1 and the CB_2 receptor. Latter receptors - the CB_2 receptors - are mainly located on immune cells in the periphery and do not produce psychoactive effect but instead suppress immune function (Atwood & Mackie, 2010). The CB_1 receptors, G protein-coupled cannabinoid receptors, are mainly found in the brain, with the highest densities found particularly in brain areas involved in mental states and cognition such as basal ganglia, cerebellum, hippocampus and cortex (Herkenham et al., 1991). Nevertheless, it has been suggested that the response to cannabinoids varies depending on the specific brain area (Romero, Garcia, Fernandez-Ruiz, Cebeira, & Ramos, 1995), e.g. one feature of cannabinoid signalling in the brain is the lack of correlation between the CB_1 density and the efficiency of receptor coupling, which may explain why responses can be triggered even in brain regions sparse of CB_1 receptors (Pacher, Bátkai, & Kunos, 2006). To date, five endocannabinoids (eCBs) have been identified, the two most intensively studied being anandamide (N-arachidonylethanolamide [AEA]) – discovered in 1992 (Devane et al., 1992) – and 2-arachidonoylglycerol (2-AG) – discovered in 1995 (Mechoulam et al., 1995). eCBs are synthesised by neurons in the cerebellum, pyramidal neurons hippocampus and cortex, medium spiny neurons in the striatum and dopaminergic neurons in the midbrain (Freund, Katona, & Piomelli, 2003). They act as retrograde messenger and are released "on demand" postsynaptically, binding to presynaptic receptors and thereby regulating both the

excitatory and inhibitory neurotransmission. Unlike conventional neurotransmitters that are stored in vesicles, cannabinoids are released "on demand" from lipid precursors (Piomelli, 2003).

Among the more than 100 different cannabinoids identified today (M. ElSohly & Gul, 2014), only THC has been shown to have psychoactive properties. Most of the psychoactive effects of THC are mediated through activation of CB_1 receptors, located mainly at the terminals of peripheral and central neurons, on either pre-synaptic glutamatergic or GABAergic neurons, resulting in a decrease in either glutamate or gamma-aminobutyric acid (GABA) release (cf. *Figure 6.* below). Numerous studies have shown that the activation of CB_1 receptors also play a role in modulating neurotransmitters such as dopamine – affecting its release indirectly via CB_1-dependent inhibition of glutamate release into GABAergic neurons in the nucleus accumbens and the ventral tegmental areal (VTA) (Fakhoury, 2016; Kuepper et al., 2013; R. Pertwee, 2008). This might explain the only modest effect of THC on dopaminergic signalling reported by acute challenge studies in humans and animals [cf. Sami, Rabiner, and Bhattacharyya (2015) for a systematic summary of studies]. This pathway has attracted a substantial attention in research on psychiatric disorders, considering that the administration of THC has been linked to psychotic symptomatology and that dopamine is thought to play a major role in psychosis pathophysiology (Howes & Kapur, 2009). The exogenous cannabinoids, as well as related synthetic compounds (e.g. naboline), bind to the cannabinoid receptors on the presynaptic neuron and mimic the endogenous synaptic modulatory effect. It has been suggested that exogenous overstimulation of CB_1 receptor on GABAergic and glutamatergic terminals from the brain stem to the striatum represents a pathway by which THC induces psychotic-like symptoms (P. D. Morrison & Murray, 2009). Cannabidiol (CBD), the other main cannabinoind present in

the cannabis plant, exhibits much lower affinity for CB_1/CB_2 and its actions have been attributed to inhibition of anandamide degradation or its interaction with as yet unidentified cannabinoid receptors (Pacher et al., 2006). CBD appears to be able to antagonize cannabinoid CB_1/CB_2 receptor agonists in animals and humans, for which reason CBD has also been described as an "inverse agonist" (R. G. Pertwee, 2005). For instance, CBD has been shown to ameliorate some of the psychotomimetic effects induced by THC (Sagnik Bhattacharyya et al., 2010a).

Figure 6. Endocannabiniod synaptic signalling



Taken from Kuepper et al. (2013): The convergence of dopamine and the endocannabinoids in the VTA:

A. Firing patterns in midbrain dopaminergic (DA) neurons are influenced by a host of excitatory (glutamatergic, GLU, as indicated in grey) and inhibitory (GABAergic, GABA, as indicated in grey) inputs. DA neurons regulate neighboring pre-synaptic terminals via retrograde endocannabinoid (2-AG, as indicated in blue) signaling.
B. When exogenous cannabinoids (THC, as indicated by cannabis leaves) bind to CB_1 receptors located on glutamatergic (GLU) and GABAergic (GABA) terminals, retrograde endocannabinoid signaling (2-AG, as indicated in blue) is disrupted and stimulation of CB_1 receptors by THC inhibits glutamate and GABA release.

2.3 TYPES OF CANNABIS

Cannabis is not a homogenous drug - by now, more than 500 different natural chemical constituent have been identified within the plant and more than 100 of them are considered to be cannabinoids (M. ElSohly & Gul, 2014). The main cannabinoids that have been investigated in research are mainly THC and CBD, although there is now growing interest in delta-9-tetrahydrocannabivain (THCV). THC, the psychoactive ingredient of cannabis, has been suggested to cause psychotic-like effects and cognitive disturbances during acute intoxication [(Sagnik Bhattacharyya et al., 2009) & see **Chapter 2.4** for a summary on acute effects]. THC is a partial agonist at CB_1 receptors, while CBD has little affinity for these. There is now a particular interest in cannabinoid receptor antagonists or reverse agonists given their ability to inhibit THC-induced hyperactivity of the eCB. Among them, CBD has been shown to reverse some of the adverse effects of the acute administration of THC, including psychotic symptoms (Sagnik Bhattacharyya et al., 2010a), impairments in perception of emotional expression (Hindocha et al., 2015) and cognitive impairments (Englund et al., 2015). CBD may also have antipsychotic properties (Leweke et al., 2012). CBD is thought to have neuroprotective effects and perhaps minimise the harmful effects on hippocampal volume present in long-term cannabis users (M Yücel et al., 2016). Other neuroimaging studies have documented opposing effects of THC and CBD on brain activation during cognitive testing, such as in the striatum during recall and the amygdala during an emotional response task (Sagnik Bhattacharyya et al., 2010a). CBD has therefore been described as a functional antagonism of CB_1 signalling (R. Pertwee, 2008).

The varieties of cannabis forms typically available in the street are traditional imported herbal cannabis (marihuana or grass) (cf. *Table 4.* below), home grown

sensimilla (without seeds) or herbal smelling “skunk”, resin (hash or hashish) and, since recently, synthetic cannabis.

Table 4. Visual depiction of different types of cannabis

Herbal cannabis[a]	Sinsemilla[b]
	
Resin[c]	**Synthetic[d]**
	

[a] Herbal (“traditional”) cannabis (Marijuana in US) [picture from Hardwick and King (2008)]
[b] Herbal home grown cannabis (“Sinsemilla”) [picture from Sirius (2016)]
[c] Resin (hash, hashish in US) [picture from Lochfoot (2016)]
[d] Synthetic cannabis (“legal highs”) [picture taken from Von Teese (2016)]

The different types of cannabis, their characteristics, as well as their average potency are summarized below in *Table 5.* and *Table 6*. The potency of cannabis [defined as the concentration (%) of THC or THC:CBD ratio] has increased over time (Burgdorf, Kilmer, & Pacula, 2011; M. A. ElSohly et al., 2016; Mehmedic et al., 2010; Niesink, Rigter, Koeter, & Brunt, 2015) . For instance, while samples of traditional herbal/skunk-type cannabis collected in the 1990th had an average THC content of 3%-5% / 5%-6% and a detectable content of CBD (~0.2%) (Burgdorf et al., 2011; Mehmedic et al., 2010), samples collected in the 2000th have up to 12%/20% and almost no visible CBD content (Burgdorf et al., 2011; Niesink et al., 2015). The rise of potency has been suggested to be the result of various factors, including selective breeding of specific cannabis strains high concentration of THC, a preference for the female plants and the consumption of more potent parts of the plant (e.g. buds instead of leafs), the usage of indoor cannabis cultivation and the purchase of seeds and equipment from the internet (Swift, Wong, Li, Arnold, & McGregor, 2013). Although the cannabis plants have generally a low CBD content, its concentration has declined even further in the recent years, leading to an increase in the THC:CBD ratio (M. A. ElSohly et al., 2016).

Table 5. Types of botanic cannabis and their classification

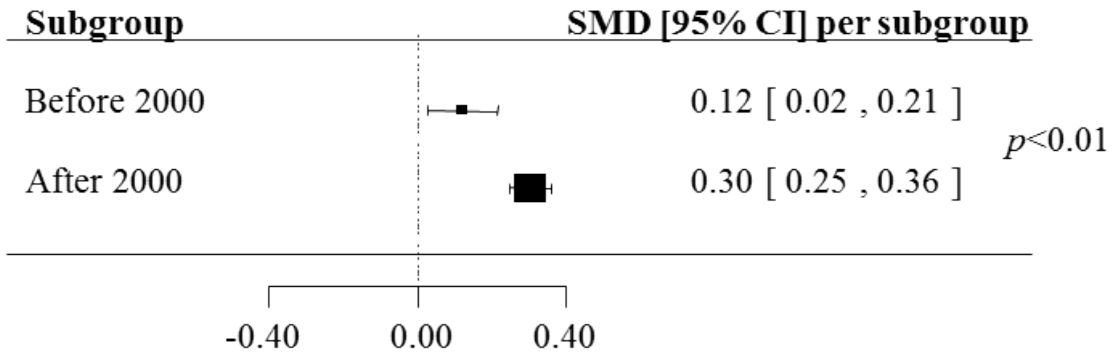
Herbal "traditional" cannabis	**Mehmedic et al. (2010):** - loose material (loose cannabis plant material with leaves, stems, and seeds - cannabis plant material consisting primarily of leaves - kilo bricks (compressed cannabis with leaves, stems, and seeds) - buds (flowering tops of female plants with seeds) **Niesink et al. (2015):** - consists of fresh or dried leaves and flowering tops but excludes the stalk, roots and seeds **Zamengo, Frison, Bettin, and Sciarrone (2015) and Tsumura et al. (2012)** - leaves (loose material without buds) - buds with seeds - whole cannabis plants **Bruci et al. (2012)** - different parts of the female plants (flowers, leaves, seeds, stems and roots, flowering tops) that is grown outdoor **M. A. ElSohly et al. (2016):** - male or female cannabis - pressed cannabis made of leaves, heads, stems, and seeds **Potter, Clark, and Brown (2008)** - the dried leaves and flowering plants of the (pollinated) female cannabis plant
Herbal home grown cannabis ("Sinsemilla")	**Mehmedic et al. (2010):** - flowering tops of unfertilized female plants with no seeds **Zamengo et al. (2015) and Tsumura et al. (2012)** - buds without seeds (sinsemilla) **Niesink et al. (2015):** - Nederwiet (dutch for "skunk), including the viarieties White Widow, K-2, Power Plant, Amnesia Haze, Jack Herrer) **M. A. ElSohly et al. (2016):** - female cannabis plants that have not been pollinated - may grow from cutting or from seed - may contain some seed (if unpollinated, the seed will be sterile) **Hardwick and King (2008)** - grown indoors from selected seed varieties and propagation of female plant cuttings using artificial lighting, heating, and control of day-length
Resin (hash, hashish in US)	**Mehmedic et al. (2010):** - composed of the resinous parts of the flowering tops of cannabis - mixed with some plant particles and shaped into a variety of forms, e.g., balls, sticks, or slabs. - generally hard with a dark green or brownish colour **Niesink et al. (2015):** - the material produced by separating the resinous parts of the flowering tops from the other vegetable matter **M. A. ElSohly et al. (2016):** - concentrated resin cake or ball produced from pressed kief - the detached trichomes and fine material that falls off the cannabis flowers and leaves - varies in color from black to golden brown depending on the purity and variety of cultivar from which it was obtained

Table 6. THC/CBD content in different types of cannabis samples over time

Study	Country	Year collected	% THC	% CBD
Herbal ("traditional") cannabis				
Mehmedic et al. (2010)	US	1993	3%	0.2%
Burgdorf et al. (2011)	US	1996	5%	0.2%
Potter et al. (2008)	UK	2005	2%	<0.10%
Niesink et al. (2015)	NL	2005	7%	1%
Mehmedic et al. (2010)	US	2008	6%	<0.10%
Hardwick and King (2008)	UK	2008	8%	<0.10%
Burgdorf et al. (2011)	US	2008	12%	<0.10%
Bruci et al. (2012)	Albania	2010	8%	1%
Tsumura et al. (2012)	Japan	2010	3%	0.1%
Tsumura et al. (2012)	Japan	2010	7%	0.3%
Niesink et al. (2015)	NL	2015	7%	1%
Zamengo et al. (2015)	Italy	2013	8%	-
Herbal cannabis ("Sinsimilla/Skunk")				
Mehmedic et al. (2010)	US	1993	6%	0.2%
Burgdorf et al. (2011)	US	1996	5%	0.2%
Potter et al. (2008)	UK	2005	14%	<0.10%
Niesink et al. (2015)	NL	2005	20%	<0.10%
Mehmedic et al. (2010)	US	2008	12%	<0.10%
Hardwick and King (2008)	UK	2008	16%	<0.10%
Burgdorf et al. (2011)	US	2008	12%	<0.10%
Swift et al. (2013)	Australia	2010	15%	<0.10%
Tsumura et al. (2012)	Japan	2010	11%	0.1%
Zamengo et al. (2015)	Italy	2013	11%	-
Niesink et al. (2015)	NL	2015	17%	<0.10%
Resin (hashish)				
Niesink et al. (2015)	NL	2005	17%	2%
Niesink et al. (2015)	NL	2015	18%	2%
Mehmedic et al. (2010)	US	1993	7%	4%
Mehmedic et al. (2010)	US	2008	24%	2%
Zamengo et al. (2015)	Italy	2010	6%	-
Zamengo et al. (2015)	Italy	2013	10%	-
Hardwick and King (2008)	UK	2008	6%	4%

Interestingly, my meta-analysis (Schoeler et al., 2015) indicated that the change of cannabis over time might be linked to adverse consequences for cannabis users. For instance, the memory impairments present in cannabis users were less prominent in earlier studies (published before the year 2000) than in more recent studies (published between 2000 and 2015) (cf. *Figure 7.* below). Although rather speculative, this difference in the memory-impairing effect linked to cannabis across time could perhaps be related to the rise in potency in the last decade.

Figure 7. Cannabis and memory: Changes in impairments over time



Note. Taken from Schoeler et al. (2015) (cf. Paper 5, Appendix I): Before 2000 = if study was published before the year 2000; After 2000 = if study was published after the year 2000; *p*=estimated significance level the categorical moderator year of publication (before 2000 vs. after 2000); SMD = Standardized Mean Difference in memory outcome between non-users and cannabis users, with larger SMD reflecting worse performance in cannabis users.

Historically, the main ways of preparation of cannabis in the UK fall broadly into two categories, cannabis resin or herbal cannabis, while cannabis oil (the concentrated extract from the cannabis plant) is less prevalent (Hardwick & King, 2008). In recent years, there was an increase in the use of herbal cannabis as opposed to the previously more commonly used resin (or Hash/Hashish in the US) (Hardwick & King, 2008). Nowadays, this type of cannabis has usually higher levels of CBD and lower levels of THC when compared to herbal cannabis (Hardwick & King, 2008).

Herbal cannabis may be further divided into two groups, including traditional herbal cannabis (derived from the pollinated female plant) and higher potency cannabis such as skunk (also called sinsemilla) (Potter et al., 2008). Sinsemilla is derived from the unpollenated (unseeded; sinsemilla=without seeds) females cannabis plant. As shown in *Table 6.*, samples identified as sinsemilla generally have the highest levels of THC and low concentrations of CBD. Recently, the user's preferences have changed from the use of traditional (seeded) herbal cannabis to sinsemilla, which appears to now dominate the UK market (Hardwick & King, 2008).

The most recent trend is the use of synthetic cannabis (SC), whose recreational use has increased in recent years (Wells & Ott, 2011). Synthetic cannabis products are legal (therefore called "legal highs") due to their structural dissimilarity to THC. However, they produce effects that resemble those of traditional cannabis since they exert their effects through the eCB. While THC is a weak partial agonist at the CB_1 receptors, the synthetic cannabinoids (e.g. HU-210, CP-55,950, WIN-55,212-2, JWH-018[naphthoylindoles], THJ-018[napthoylindazoles], AKB-045[indazole carboxamides]) are more potent full agonists at the same receptor. Although the substance is sold as cannabis-like compounds, SC is cause more negative and unpredictable effects (Winstock & Barratt, 2013) than the natural cannabis due to the uncontrollable variety of chemicals. For instance, while intoxicated, those users that consumed SC as opposed to traditional cannabis exhibited higher levels of disorientation, incoherent speech and confusion in comparison (Chase et al., 2016). On the illicit drug market, this group of psychoactive drugs is now the fastest growing group (UNODC, 2015). Commonly used products are known as "Spice", "K2" or "Kronic". This product usually contains dried and shredded plant material with no

intrinsic psychoactive ingredient, but which is sprayed with one or several synthetic cannabinoids (UNODC, 2015).

2.4 CANNABIS AND MENTAL HEALTH: ACUTE EFFECTS

In recent years, greater research has focused on investigating the acute effects of cannabis on mental states, using experimental designs such as the "gold-standard" double-blind, placebo-controlled and within-subject pharmacological challenge study. Acute effects are transient and present during the period in which the subject is intoxicated (i.e. feeling "high") with the drug, which lasts for about 5 to 200 minutes (D'Souza et al., 2004). Among the chemical constituents of cannabis, THC has been the most frequently investigated. Studies of acute effects may differ in some aspects of their methods, such as study design (within-subject vs. between-subject comparison), route of administration (oral, smoked, intravenous), the dose administered, the time-point of administration or the cannabis use history of a participants – all factors that need to be taken into account when interpreting and comparing the results across studies. In those randomized controlled trials (RCT), either a single dose or multiple doses of THC are administered and compared to the placebo condition in order to elucidate its (dose-response) effects on human behaviour and mental states and its underlying neural mechanism. Several areas of mental health related outcome have been investigated in this field of research, including mood states (e.g. depression, happiness, anxiety), perceptions (e.g. positive symptoms, dissociations), behavior (e.g. impulsivity, control inhibition) and cognition (e.g. learning and memory, emotion recognition) (cf. *Table 7.* below). This evidence is therefore crucial when evaluating potential mechanisms [i.e. biological plausibility (A. B. Hill, 1965)] by which cannabis exerts its effects on human mental health conditions such as psychosis, mood or deviant behavior (cf. **Chapter 2.5** below).

A consistent finding reported by most acute challenge studies is that THC induces positive symptoms, including in those with minimal previous cannabis exposure

(Sagnik Bhattacharyya, Atakan, et al., 2015b; D'Souza et al., 2008; Englund et al., 2015; P. Morrison et al., 2009; Radhakrishnan, Skosnik, et al., 2015; Tunbridge et al., 2015) and those who use cannabis at a regular basis (Barkus et al., 2011; Van Wel et al., 2015), implicating that the level of tolerance may not prevent from the psychotomimetic effects of smoked cannabis. Furthermore, adverse acute effects were reported by studies using lower doses of THC (e.g. ~1mg intravenous THC) (Radhakrishnan, Skosnik, et al., 2015) and higher doses of THC (~12mg smoked THC) (Van Wel et al., 2015) and those who tested for dose-response effects (D'Souza et al., 2004). However, although it was reported that THC significantly induced psychotic and dissociative symptoms in non-users as well as frequent users, the effect in frequent users was blunted, which may implicate some tolerance-effects to symptom-inducing effects of cannabis in regular users (D'Souza et al., 2008). Furthermore, the effects of THC were stronger in those with a with a pre-existing psychotic disorder when compared to healthy controlled (D'Souza et al., 2005) and were modulated by variation in genes for the dopamine transporter (DAT1/AKT1) (S Bhattacharyya et al., 2012), suggesting some genetic sensitivity to its psychoactive effects. However, it was reported that there were no significant differences between patients with psychosis, their unaffected relative and healthy controls in their subjective perceptual experiences of cannabis following THC administration (Kuepper et al., 2013). Studies also reported that the administration of THC significantly elevated levels on scales measuring negative symptoms (Barkus et al., 2011; D'Souza et al., 2004; Englund et al., 2015; Fusar-Poli et al., 2009), although the effect was not present in those who were current regular users of cannabis (Marieke Liem-Moolenaar et al., 2010).

Acute administration of THC has also consistently been linked to the production of cognitive impairments in a dose-dependent manner, including impairments in recall

(V. H. Curran, Brignell, Fletcher, Middleton, & Henry, 2002; D'Souza et al., 2004; Marieke Liem-Moolenaar et al., 2010) and working memory (Marieke Liem-Moolenaar et al., 2010; McDonald, Schleifer, Richards, & de Wit, 2003; P. Morrison et al., 2009). Those impairments are not just present in those with minimal previous exposure (Englund et al., 2015; P. Morrison et al., 2009; Tunbridge et al., 2015), but also in those who are current regular users of cannabis (Marieke Liem-Moolenaar et al., 2010; Weinstein et al., 2008), implicating that tolerance to the cognitive-impairing effects is unlikely to occur. In this context, it has been proposed that THC affects the encoding of new memories during intoxication which then perhaps leads to the deficits in recalling those memories, while old memories that were consolidated outside the state of acute intoxication remain unaffected (H. V. Curran et al., 2016). The presence of a dose-response relationship is also supported by a study that found greater memory impairments in those users who consumed forms of cannabis with a low content of CBD when compared to forms with a higher content of CBD (C. J. Morgan, Schafer, Freeman, & Curran, 2010), suggesting that the type of the cannabis smoked plays a role with regard to the cognitive performance in users. Other evidence comes from a naturalistic observational study using Ecological Momentary Assessment (EMA, involving a seven-day monitoring period) in cannabis users, in which it was found that working memory performance was significantly worse in periods of acute use than in periods of non-use (Schuster, Mermelstein, & Hedeker, 2016). Similarly, in a naturalistic study, the effects during acute intoxication in cannabis users on working memory were moderated by genetic variations within the AKT1 gene (CJA Morgan, Freeman, Powell, & Curran, 2016), implicating that a genetic vulnerability to psychosis may modulate also modulate its effects on cognition. This is in line with experimental evidence that found greater cognitive impairments following THC administration in

patients with pre-existing psychotic disorder when compared to healthy controls (D'Souza et al., 2005). Accumulating evidence has also implicated the eCB in the perception of emotional expressions (Lafenêtre, Chaouloff, & Marsicano, 2007), an ability that is an essential aspect of appropriate social interactions and interpersonal relationships. This ability has been reported to be impaired in people with mental health problems such as depression, anxiety or schizophrenia (Phillips, Drevets, Rauch, & Lane, 2003). It has been found that the induction of cannabis significantly impaired emotion recognition in a dose-dependent manner in healthy subjects with previous cannabis experiences (Ballard, Bedi, & de Wit, 2012). Other evidence found that THC significantly reduced accuracy for stimuli with negative emotional content but not for stimuli with positive emotional content (Bossong et al., 2013). Interestingly, CBD protected against the impairments in emotional processing induced by THC (Hindocha et al., 2015).

There is also evidence that the acute intoxication of THC leads to increased levels of anxiety in those with some previous cannabis exposure (Sagnik Bhattacharyya, Atakan, et al., 2015b; Englund et al., 2015), as well as in those who are currently using (Ballard et al., 2012; Hindocha et al., 2015; Van Wel et al., 2015). Despite the anxiety-inducing that are present in both non-users of cannabis and regular users of cannabis, the effect has been shown to be stronger in those without previous regular cannabis exposure, indicating that the level of tolerance plays a role in this context (D'Souza et al., 2008). Less consistent are the results with regard to depressive symptoms. In fact, there is little ground to believe that THC acutely elicits depressive symptoms (Englund et al., 2015; Wachtel, ElSohly, Ross, Ambre, & De Wit, 2002) or results in changes in mood (Marieke Liem-Moolenaar et al., 2010), although results are somewhat mixed (Van Wel et al., 2015).

Cannabis may also indirectly exert potential negative effects on conduct by altering the system that is responsive for regulating impulses and inhibitions. Impulsive behavior can be described as a variety of maladaptive behavior, e.g. the predisposition towards rapid, unplanned reactions without regard to the negative consequences and the inability to inhibit inappropriate actions (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Some evidence from acute challenge studies is indicative of THC increasing impulsive or risk behavior in non-users (Sagnik Bhattacharyya, Atakan, et al., 2015b), regular users (Ramaekers et al., 2006) and heavy users (Weinstein et al., 2008), especially if exposed to high doses of THC (Weinstein et al., 2008). The effects seem to be present in tasks measuring psychomotor control (Weinstein et al., 2008), response inhibition (Sagnik Bhattacharyya, Atakan, et al., 2015b), as well as decision making (Weinstein et al., 2008), although the latter dimension was not impaired in all studies (Ramaekers et al., 2006).

To summarise, evidence from acute challenge studies is relative consistent with regard to its acute adverse effects on outcome such as psychosis-like symptoms, cognitive function and behavioural control, as well its anxiogenic effects, while the results regarding the acute effects on mood such as depressive symptoms are less clear. However, the acute administration only mimics the intoxication effects and leads only to sub-clinical symptoms, i.e. conclusions are limited with regard to the long-term effects within a person's natural environment. For instance, its effects are likely to depend on additional factors that are ethically often not feasible to explore in acute challenge studies in humans such as the modulating effects of pharmacological parameters (e.g. the effect of duration/chronicity of use, age of onset of use, frequency of use, abstinence from cannabis). In other words, despite the evidence suggestive of adverse effects during acute intoxication, uncertainty remains as to whether those

effects persist over the long-term. For instance, one THC challenge study reported none of the observed adverse effects on cognition and psychotic symptomatology remained following a period of abstinence when THC was no longer detectable in plasma (V. H. Curran et al., 2002; P. Morrison et al., 2009).

Table 7. Acute challenge studies investigating the effect of THC on outcome

Study	N	Dose THC (in mg)		Outcome	
Psychotic effect					
Englund et al. (2015)	10 (RC)	Single dose (IV)	1mg	Positive symptoms (CAPE)	↔
Radhakrishnan, Skosnik, et al. (2015)	27 (LC)	Single dose (IV)	1mg*	Total PANSS	↓
Tunbridge et al. (2015)	78 (LC)	Single dose (O)	1.5mg	Psychotic symptoms (CAPE)	↓
P. Morrison et al. (2009)	22 (LC)	Single dose (IV)	2.5mg	Positive symptoms (PANSS)	↓
D'Souza et al. (2004)	22 (LC)	Dose-response (IV)	2.5mg/5 mg	Positive symptoms (PANSS)	↓
D'Souza et al. (2008)	22 (LC)	Dose-response (IV)	2.5mg/5 mg	Dissociative symptoms (CADSS)	↓
Sagnik Bhattacharyya, Atakan, et al. (2015b)	36 (RC)	Single dose (O)	10mg	Positive symptoms (CAPE)	↓
Van Wel et al. (2015)	122 CC_2	Single dose (O)	12mg***	Dissociative symptoms (CADSS)	↓
Van Wel et al. (2015)	122 CC_2	Single dose (O)	12mg***	Positive symptoms (B-VAS)	↓
Barkus et al. (2011)	10 LC	Single dose (IV)	2.5mg	Positive symptoms (PANSS)	↓
Marieke Liem-Moolenaar et al. (2010)	35 (CC_2)	Dose-response (IH)	2mg/4mg/6mg	Positive symptoms (PANSS)	↓
Anxiogenic effect					
Radhakrishnan, Skosnik, et al. (2015)	27 (LC)	Single dose (IV)	1mg*	Anxious (VAS)	↔
Englund et al. (2015)	10 (RC)	Single dose (IV)	1mg	Anxiety symptoms (BAI)	↓
D'Souza et al. (2004)	22 (LC)	Dose-response (IV)	2.5mg/5 mg	Anxious (VAS)	↓
Ballard et al. (2012)	25 (CC_2)	Dose-response (O)	7.5mg/15 mg	Anxious (VAS)	↓
Hindocha et al. (2015)	48 (CC_2)	Single dose (IH)	8 mg	Anxious (VAS)	↓
Sagnik Bhattacharyya, Atakan, et al. (2015b)	36 (RC)	Single dose (O)	10mg	Anxious (STAI)	↓
Bossong et al. (2013)	11 (CC_2)	Single dose (IH)	6 mg	Anxious (VAS)	↔
Van Wel et al. (2015)	122 (CC_2)	Single dose (O)	12mg***	Anxiety symptoms (POMS)	↓
Negative symptoms					
Englund et al. (2015)	10 (RC)	Single dose (IV)	1mg	Negative symptoms (CAPE)	↓
D'Souza et al. (2004)	22 (LC)	Dose-response (IV)	2.5mg/5 mg	Negative symptoms (PANSS)	↓
Fusar-Poli et al. (2009)	15 (RC)	Single dose (O)	10mg	Negative symptoms (PANSS)	↓
Barkus et al. (2011)	10	Single dose	2.5mg	Negative symptoms	↓

	(LC)	(IV)		(PANSS)	
Marieke Liem-Moolenaar et al. (2010)	35 (CC_2)	Dose-response (IH)	2mg/4mg/6mg	Negative symptoms (PANSS)	↔
Cognitive effects (memory)					
Englund et al. (2015)	10 (RC)	Single dose (IV)	1mg	Memory (HVLT)	↓
Englund et al. (2015)	10 (RC)	Single dose (IV)	1mg	Digit Span Backwards	↔
Tunbridge et al. (2015)	(LC)	Single dose (O)	1.5mg	Digit Span Backwards	↓
P. Morrison et al. (2009)	22 (LC)	Single dose (IV)	2.5mg	Memory (RAVLT)	↓
D'Souza et al. (2004)	22 (LC)	Dose-response (IV)	2.5mg/5 mg	Memory/recall (HVLT)	↓
Fogel, Kelly, Westgate, and Lile (2016)	30 (CC_1)	Dose-response (O)	5/15mg/ 25mg	Digit-symbol substitution task	↓
V. H. Curran et al. (2002)	15 (LC)	Dose-response (O)	7.5mg/15 mg	Memory (BSRT)	↓
Weinstein et al. (2008)	14 (CC_3)	Dose-response (IH)	13mg/17 mg	Attention (WCST)	↓
McDonald et al. (2003)	37 (LC)	Dose-response (O)	7.5mg/15 mg	Attention (DSST)	↔
McDonald et al. (2003)	37 (LC)	Dose-response (O)	7.5mg/15 mg	Working memory (Digit Span)	↓
McDonald et al. (2003)	37 (LC)	Dose-response (O)	7.5mg/15 mg	Memory/Learning (HVLT)	↔
Marieke Liem-Moolenaar et al. (2010)	35 (CC_2)	Dose-response (IH)	2mg/4mg/6mg	Memory/Learning (VVLT)	↓
Impulsive/risk behaviour – inhibitory control					
Sagnik Bhattacharyya, Atakan, et al. (2015b)	36 (RC)	Single dose (O)	10mg	Go/No-Go	↓
Ramaekers et al. (2006)	20 (CC_2)	Dose-response (IH)	18mg/35 mg**	Critical tracking task	↓
Ramaekers et al. (2006)	20 (CC_2)	Dose-response (IH)	18mg/35 mg**	Stop signal task	↓
Ramaekers et al. (2006)	20 (CC_2)	Dose-response (IH)	18mg/35 mg**	The Iowa gambling task	↔
Weinstein et al. (2008)	14 (CC_3)	Dose-response (IH)	18mg/35 mg**	Gambling task	↓
McDonald et al. (2003)	37 (LC)	Dose-response (O)	7.5mg/15 mg	Impulsivity (Go/No-Go)	↔
McDonald et al. (2003)	37 (LC)	Dose-response (O)	7.5mg/15 mg	Impulsivity (ST)	↔
Depression/mood					
Englund et al. (2015)	10 (RC)	Single dose (IV)	10mg	Depressive symptoms (CAPE)	↔
Van Wel et al. (2015)	122 CC_2	Single dose (O)	12mg***	Depressive symptoms (POMS)	↓
Wachtel et al. (2002)	13 (LC)	Dose-response (IH)	10mg/13 mg	Mood (POMS)	↔

Marieke Liem-Moolenaar et al. (2010)	35 (CC_2)	Dose-response (IH)	2mg/4mg/6mg	Mood (VAS)	↔
Emotion recognition					
Ballard et al. (2012)	25 (CC_2)	Dose-response (O)	7.5mg/15 mg	Facial emotion recognition task	↓
Hindocha et al. (2015)	48 (CC_2)	Single dose (IH)	8 mg	Emotional processing task	↓
Bossong et al. (2013)	11 (CC_2)	Single dose (IH)	6 mg	Emotional processing task	↓

Note. CC_1 (Current cannabis user); CC_2(>monthly use/current); CC_3(>daily use/current); LC (lifetime cannabis use >1); RC (regular lifetime cannabis use <25); O (Oral); IV (Intravenous), IH (Inhaled)

↓ = Poor outcome (reduced cognition, higher positive/negative symptom severity, higher depression/anxiety, increased dissociation)

↔ = No effect of acute administration when compared to placebo

* administration of 0.15 mg/kg (10.5mg in a 70 kg individual)

** administration of 0.25 and 0.5 mg/kg (17.5mg/35mg in a 70 kg individual)

*** administration of 0.30 mg/kg (12mg in a 70 kg individual)

2.5 Cannabis and mental health: Long-term effects

2.5.1 Introduction

While most adolescent cannabis use remains experimental, an incidence of increased cannabis use typically occurs within the period of early adolescence to late adolescence (Coffey, Lynskey, Wolfe, & Patton, 2000). It has been estimated that about 1 out of 10 individuals goes on to develop a cannabis use disorder (CUD) following the first use (Hall & Pacula, 2003). In particular, early onset and frequent use of cannabis during adolescence have been identified as risk factors for later ongoing problematic cannabis use, other drug and substance use problems, mental health conditions, as well as delinquency, risky behaviour and criminal offending (Feingold, Weiser, Rehm, & Lev-Ran, 2015; David M Fergusson, Horwood, & Swain‐Campbell, 2002; Schoeler, Monk, et al., 2016; Swift, Coffey, Carlin, Degenhardt, & Patton, 2008). However, causality in this context has often been questioned, since there is the concern that those individuals initiating cannabis use at an early age may already be psychopathological different from their non-using peers before initiating cannabis use, e.g. are more likely to exhibit antisocial and non-conformist behavior, affiliating with drug-using peers, perform poorly at school and comprise genetic vulnerability to initiate cannabis use (Coffey et al., 2000; Copeland & Swift, 2009; Hall & Degenhardt, 2007; R. A. Power et al., 2014).

With regard to mental health correlates, those individuals seeking treatment for a cannabis use disorder (CUD) are at high risk to have at least one other comorbid psychiatric diagnosis (~60%-94%, cf. *Table 8.* below) and a substantial proportion (~14%) was found to be diagnosed with more than 3 comorbid conditions (Norberg, Battisti, Copeland, Hermens, & Hickie, 2012). Within samples of individuals diagnosed with CUD, the highest rates of comorbidity seem to be present for anxiety and mood

disorders (Dorard, Berthoz, Phan, Corcos, & Bungener, 2008; Guillem, Arbabzadeh-Bouchez, Vorspan, & Bellivier, 2015; Norberg et al., 2012; Oliveira & Malbergier, 2014), followed by psychotic disorders (Guillem et al., 2015; Norberg et al., 2012; Oliveira & Malbergier, 2014). Although those prevalence rates may indicate that cannabis is a drug linked to mental health problems in general and has a rather non-specific effect with regard to outcome, those cross-sectional studies are only of limited interpretability when evaluating causal effects of cannabis on mental health outcome. For instance, one problem that arises is that there is no assertion as to whether the diagnosis of an Axis I disorder preceded the diagnosis of CUD or whether the receipt of the diagnosis was a subsequent event. For instance, in a recent study Farmer et al. (2016) reported that the estimates for precursory comorbidity (disorders that had their onset prior to CUD) were higher than the estimates for ensuing comorbidity (disorders that had their onset following the onset of CUD) for mood disorders (26% vs. 16%) and anxiety disorders (7% vs. 3%), which indicates that a proportion of comorbid psychiatric diagnoses linked of CUD could be result of reverse causation. Furthermore, a study that compared CUD prevalence rates across different psychiatric disorders reported that the lifetime presence of CUD was highest in subjects with schizophrenia (21%), which was higher when compared to bipolar disorder (6%) and depression (2%) (Heilbronner et al., 2015).

Hence, in the following paragraphs I will review the literature investigating the effects of cannabis on the most commonly investigated outcomes, including cognition, anxiety and affective disorders, deviant behavior and substance use disorders, before taking a closer look at the relationship between cannabis use and risk of onset of psychosis.

Table 8. Comorbid psychiatric diagnoses in patients with cannabis use disorder

Study	N group	Comorbid diagnosis	%
Norberg et al. (2012)	36 CUD	Other SUD	22%
		Mood disorder	66%
		Psychotic disorder	28%
		Anxiety disorder	61%
		Childhood disorder	0%
Oliveira and Malbergier (2014)	80 CUD	Mood disorder	23%
		Anxiety disorder	20%
		Schizophrenia	9%
Notzon et al. (2016)	99 CUD	Childhood disorder (ADHD)	34%
Farmer et al. (2016)	173 CUD before 30	Mood disorder	61%
		Anxiety disorder	14%
		Other SUD	70%
Guillem et al. (2015)	207 CUD	Mood disorder	38%
		Anxiety disorder	53%
		Psychotic disorder	5%
Dorard et al. (2008)	32 CUD	Mood disorder	63%
		Anxiety disorder	38%
		Psychotic disorder	0%

N = Number of subjects

First, one area of great interest in research on cannabis use is the question that is concerned with cognitive outcome linked to the use. There is now accumulating evidence that has linked long-term and heavy cannabis use to poor neuropsychological performance (Schoeler & Bhattacharyya, 2013). Recent meta-analyses reported that there are small but aversive effects of cannabis on global neurocognitive performance (d=0.14) following a period of abstinence (Schreiner & Dunn, 2012), with more pronounced impairments being present if started at an earlier age (Ganzer, Bröning, Kraft, Sack, & Thomasius, 2016). Similarly, the results from my meta-analysis (Schoeler, Kambeitz, et al., 2016), in which I investigated the effects of cannabis use on memory function, suggest that cannabis use had a robust but modest adverse effect on global memory function as well as its multiple component dimensions in cannabis users, with the precise magnitude of the effect depending on the specific dimension of

memory tested. There is also evidence in support of a dose-response relationship in this context. For instance, cognitive impairments increased with increasing frequency of use, longer duration of use and earlier age of onset of use (V. H. Curran et al., 2002; Fried, Watkinson, & Gray, 2005; Lisdahl, Gilbart, Wright, & Shollenbarger, 2015; Tapert, Schweinsburg, & Brown, 2008). Only a few longitudinal studies investigated the course of cannabis use and with regard to changes in cognitive function. For instance, one study has linked ongoing cannabis use to a decline in IQ which was not present in non-users (N. J. Jackson et al., 2016). Meier et al. (2012) reported that the level of persistence of heavy cannabis use throughout the time of follow up was significantly linked to a decline in IQ , processing speed and verbal memory, while taking into consideration the level of pre-cannabis IQ, acute effects of cannabis, other illicit drug us and alcohol. Although this study seem to provide relatively robust evidence in support of cannabis as a causal risk factor for neurocognitive impairments, it has been argued out that this association was possibly due to uncontrolled confounding and may reflect an over-estimation of effects (Rogeberg, 2013). For instance, a recently published study investigating the longitudinal effects of cannabis, in which a sibling-design was employed, found that the adverse effects of cannabis on IQ over time disappeared when controlled for genetic confounding, which may indicate that there is a genetic and/or family-environmental predisposition to both decline in IQ and initiation of cannabis use, which would mean that the association between cannabis and cognitive decline is the result of a "shared-vulerability" (N. J. Jackson et al., 2016).

Another area of interest in the context of cannabis and mental health outcome is its relation with anxiety and affective disorders. The results from my meta-analysis (Schoeler, Kambeitz, et al., 2016), in which I compared the depression scores between cannabis users and non-users, indicated that cannabis user were characterised by

significantly higher depression scores. However, this cross-sectional summary does not allow drawing conclusions regarding the causal effects of cannabis. Unlike the acute effects of cannabis that are present for outcome such as psychotic symptoms or cognitive impairments (cf. **Chapter 2.4** above), cannabis may not exerts its effects immediately (acutely) with regard to depression and its adverse effects on mood may only become present following long-term continued/chronic use. For instance, experimental studies did not find that the administration of THC increased depressive symptoms in healthy subjects (Englund et al., 2015; Wachtel et al., 2002). Similarly, within 6 months of follow up, changes in cannabis use were not significantly related to changes in depressive symptomatology (Park et al., 2015). Another study looking at the effects of cannabis potency and depressive symptoms reported that the THC:CBD ratio in the cannabis consumed was not linked to depression scores in cannabis users (Schubart et al., 2011). Studies that have explored dose-response relationships reported both the absence of effect of frequency of cannabis use on depression (Feingold et al., 2015; Repetto, Zimmerman, & Caldwell, 2008) and the presence of a dose-response relationship between cannabis use and depression (D. W. Brook, Brook, Zhang, Cohen, & Whiteman, 2002; Suzanne H Gage et al., 2015). In a longer follow up, integrating data from 4 different cohorts, Horwood et al. (2012) reported that two of the cohorts suggested that cannabis use leads to the development of depression (Anstey et al., 2011; David M. Fergusson & Horwood, 2001), a third cohort suggested that depression leads to cannabis use (Patton et al., 2007) while the fourth one did not find that either of those relationships were significant when employing longitudinal modelling (Prior, Sanson, Smart, & Oberklaid, 2000). The lack of clear evidence with regard to depression outcome may be linked to the main limitations of evidence to date, which is the absence of a life-span prospective design, the non-consideration of important confounders and

the non-exploration of the direction of association. Hence, in order to address those limitations, I recently analysed data from the Cambridge Study of Delinquent Development (CSDD) study, in which boys were followed up from age 8 to 48 years, which allowed me to prospectively investigate the association between cannabis use and risk of Major Depressive Disorder (MDD) (cf. **Paper 8** (Schoeler et al., under review), Appendix I). Here, I found that early onset cannabis use (before age 18) but not late onset cannabis use (after age 27) was associated with a higher risk of a subsequent diagnosis of MDD diagnosis, while controlling for observed (e.g. other illicit drug use and presence of other mental health diagnoses) and non-unobserved time-invariant factors (e.g. shared genetic or stable environmental factors). This is consistent with evidence from animal research, in which long-term exposure of cannabinoids resulted in depression-like symptoms only in adolescent but not adult rats (Bambico, Nguyen, Katz, & Gobbi, 2010), which is in further support of a neurodevelopmental sensitivity to the adverse effects cannabis use in this context.

Adverse effects following cannabis use have also been implicated with regard to risk of suicide; a recent meta-analysis concluded that heavy cannabis use also increased the risk for suicide (Borges, Bagge, & Orozco, 2016), even when adjusted for confounders such as other illicit drug and alcohol use and history of depression. When assessing both directions over a period of 30 years, it was found that frequency of cannabis use was linked to subsequent suicidal ideation, while the reverse direction (suicidal ideation as a predictor for initiation of cannabis use) was not significant (Jan C. van Ours, Williams, Fergusson, & Horwood, 2013). The link to suicidality also remained when controlled for time-invariant unobserved sources of confounding. For instance, using a discordant twin design, cannabis use prior age 17 was linked to suicidal attempts (Lynskey et al., 2004). Similarly, in another study that used a fixed-

effects design (i.e. the adoption of the discordant twin design), it was reported that in periods of heavier use there was a higher risk of suicidal ideation and suicide attempts when compared to periods in which cannabis was not used or was used less frequently (David M Fergusson et al., 2002). This would indicate that the relationship between cannabis use and risk of suicide cannot be explained solely by shared genetic or stable environmental influences.

With regard to anxiety disorders, a recent meta-analysis found that cannabis significantly predicted anxiety disorders (Kedzior & Laeber, 2014), although wider conclusions are limited by the mainly cross-sectional nature of the studies included. It has also been reported that cannabis use predicted the subsequent emergence of anxiety disorders in longitudinal studies (Whiteford et al., 2013), but this finding has not been replicated in a recent longitudinal study (Blanco, Hasin, Wall, & et al., 2016). Several lines of investigations have raised doubts as to whether there is a causal relationship. For instance, it was reported that the risk for subsequent anxiety in cannabis use did not persist beyond the effect of co-occurring cigarette use, implicating that this factor may play a role within this association (Zvolensky et al., 2008). Furthermore, longitudinal evidence in an age-mixed population (aged 20-64) reported that cannabis use was not predictive of subsequent anxiety but that anxiety predicted subsequent onset of cannabis use (Danielsson, Lundin, Agardh, Allebeck, & Forsell, 2016), suggesting that reverse causation has to be considered as one potential explanation for the high rates of anxiety disorders found in individuals with CUD (Dorard et al., 2008; Farmer et al., 2016; Guillem et al., 2015; Norberg et al., 2012; Oliveira & Malbergier, 2014). Studies that looked at multiple outcomes together reported either no significant effects of cannabis on subsequent risk of anxiety and depression (Blanco et al., 2016; Danielsson et al., 2016) or provide rather mixed results. For instance, in controlled models, the effects of

cannabis on incidence of psychiatric disorders remained significant for MDD and bipolar disorder but not anxiety disorders (Van Laar, Van Dorsselaer, Monshouwer, & De Graaf, 2007). To the contrary, it was found that frequency of adolescent cannabis use predicted subsequent adulthood anxiety but not depression (Whiteford et al., 2013). Inconsistent with studies reporting uni-directional effects of cannabis on affective disorders, a 10-year prospective study reported that the presence of anxiety disorders, depression and substance use disorders significantly predicted the incidence of cannabis use (any use) and development of CUD (Wittchen et al., 2007). Furthermore, other drug use may play an important role with regard to mood and anxiety disorders. For instance, it was reported that frequency of cannabis use was not linked to depressive symptoms or symptoms of anxiety in a sample of polystimulant dependent users – instead, those outcomes were linked to frequency of cocaine use and alcohol use (Willi et al., 2016). Although evidence from epidemiological research remains inconclusive as to whether (non-acute) cannabis use is in fact a risk factor for the development of anxiety disorders, experimental evidence implicate that cannabis use may acutely induces anxiety, e.g. the acute administration of THC increased levels of anxiety in those will little previous cannabis exposure (Sagnik Bhattacharyya, Atakan, et al., 2015b; Englund et al., 2015), as well as in those who are currently using (Ballard et al., 2012; Hindocha et al., 2015; Van Wel et al., 2015) and evidence from animal research is suggestive of increased anxiety-like symptoms as a result of long-term exposure of cannabinoids in adolescent rats (Bambico et al., 2010).

Cannabis use also been investigated with regard to the development of "problem behavior" such as psychosocial difficulties, deviant behavior or other substance use disorders. For instance, there is experimental evidence suggestive of a dose-response relationship between the dose of the THC administered and impairments in decision

making (Weinstein et al., 2008), which could implicate cannabis as a potential risk factor for impulsive behavior and deviant behavior. Cross-sectional observational evidence also suggested that poorer decision making skills were linked to the level of severity of CUD symptomatology (Gonzalez et al., 2012). Longitudinal studies reported that adolescent cannabis use was linked to subsequent work and school difficulties (J. S. Brook, Brook, Rosen, & Rabbitt, 2003) and fewer years of completed education (Jan C Van Ours & Williams, 2007). Similarly, a recent study that looked at frequency of cannabis use reported significant dose-response relationships between adolescent cannabis use and outcome young adulthood, including reduced likelihood to complete highschool, increased risk of subsequent illicit drug and cannabis abuse and higher risk of suicide (Silins et al., 2014). In this context, pprevious research has also shown that violent behavior (Johnson, Wish, Schmeidler, & Huizinga, 1991; Monshouwer et al., 2006; Nabors, 2010; E. N. Peters, Schwartz, Wang, O'Grady, & Blanco, 2014) or delinquency and aggression in adolescence may result from cannabis use. In a recently published paper [**Paper 7**(Schoeler, Theobald, et al., 2016), Appendix I], I examined whether '*continued use*' is the critical determinant that underpins the association between cannabis use and violence. I found that compared with never-users, continued exposure to cannabis (use at age 18, 32 and 48 years) was associated with an increased risk of subsequent violent behavior, while taking into consideration time-varying and time-invariant factors of confounding and the effect of reverse causation. Therefore, long-term cannabis exposure may cause impairments in response inhibition resulting in behavioral control in vulnerable individuals that may underlie impulsive, violent behaviour, by altering the normal functioning of its underlying neural substrate, the ventrolateral prefrontal cortex in man (S. Bhattacharyya et al., 2014).

Finally, relative consistent evidence exists with regard to the relationship between cannabis use and the risk of being diagnosed with subsequent other substance use disorders. For instance, in a follow up study, it has been reported that CUD at T1 predicted the incidence of alcohol used disorder (AUD) at T2 (in those with no prior AUD) and predicted persistence of AUD (in those with prior AUD) (Weinberger, Platt, & Goodwin, 2016). This was replicated in a recent study that reported a link between adult frequency of cannabis use and risk of subsequent development of AUD, other SUD and cigarette dependence (Blanco et al., 2016). Hence, the evidence summarised here indicates that cannabis use in adolescence may be a risk factor for later-life "problem behavior", which might be driven by a use pattern that reflects a continuous, early onset and high-frequency use throughout the life span.

2.5.2 CANNABIS AND THE DEVELOPMENT OF PSYCHOSIS

Although the link between cannabis and psychosis has already been reported almost 70 years ago (Ames, 1958), it did not became the focus of further attention since the first longitudinal study published in the 80th (Andréasson, Engström, Allebeck, & Rydberg, 1987), which reported that there were increased cases of cannabis users seen in patients referred for their first episode psychosis. Today, there is consistent evidence that the rates of cannabis users seen in FEP are substantially higher than those estimated in the general population (Degenhardt & Hall, 2001; Di Forti, Marconi, et al., 2015). Several meta-analyses have concluded that cannabis use significantly increased the risk for developing psychosis roughly by the odds of two (T. H. Moore et al., 2007), and a meta-analysis investigating dose-response relationships reported an increase in risk by the odds of 4 for the most severe cannabis users (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016). Hence, in accordance with the concept of causality (A. B. Hill, 1965),

several lines of evidence suggest that the effect of cannabis on risk of psychosis is present in a dose-dependent manner. To illustrate, population studies reported that those users who had a higher THC:CBD ratio reported significantly more psychotic symptoms than those with a low ratio (Schubart et al., 2011). Similarly, a recent study reported that 24% of cases with a first episode could be attributed to the use of high-potency (skunk-type) cannabis around the time of onset, independent from cigarette, alcohol and other drug use (Di Forti, Marconi, et al., 2015). Another study found that heavy users of cannabis (daily) prior to the onset were more likely to experience an acute mode of onset (as opposed to non-acute) when compared to those who used it less frequently (Compton, Broussard, Ramsay, & Stewart, 2011). It was also reported that duration of cannabis use predicted psychotic symptoms (J. McGrath et al., 2010) – in fact, has been suggested that the duration of exposure from early adolescence may underlie the emergence and persistence of psychotic symptoms (Kuepper et al., 2011b). Furthermore, other studies found that cannabis use predicted an earlier age of onset of psychosis (Large, Sharma, Compton, Slade, & Nielssen, 2011; N. C. Stefanis et al., 2013) and that this effect was more prominent in those who used it heavily (Di Forti et al., 2014; N. C. Stefanis et al., 2013), in those who used high-potency (skunk-type) forms of cannabis (Di Forti et al., 2014) and if cannabis was started at an earlier age (Leeson et al., 2012). Age of onset of cannabis use was reported to directly predict age of onset of psychosis and age of first hospitalisation, while the mean between first cannabis use and onset of psychosis was found to be 7 years (Galvez-Buccollini et al., 2012). Studies in individuals at high-risk reported that the (unadjusted) risk of transition to psychosis following the help-seeking presentation was 3.4 times higher in those who continued compared to those who discontinued (19% vs. 6%) (Valmaggia et al., 2014). In other patient samples in which psychotic features are common, cannabis was also

found to be linked to psychotic symptomatology. For instance, it was reported in a sample of patients with bipolar disorder that the presence of a lifetime cannabis use disorder significantly predicted the presence of a lifetime psychotic episode (Braga, Burdick, DeRosse, & Malhotra, 2012) and that comorbid CUD in bipolar disorder was associated with the presence of psychotic features when admitted to the hospital (Weinstock, Gaudiano, Wenze, Epstein-Lubow, & Miller, 2016). Hence, unlike the results from cannabis research with regard to other mental health outcomes (cf. above **Chapter 2.4**), there is a rarely seen consistency in findings across epidemiological studies investigating (dose-response) effects of cannabis on risk of subsequent psychosis, which has been used as a strong argument to raise concerns regarding the risks associated with heavy cannabis use in the general population, especially in light of the increase in potency over time (M. A. ElSohly et al., 2016), the increase in prevalence of cannabis use in recent years (Hasin et al., 2015) and the high prevalence rates especially in young people (UNODC, 2014). Nevertheless, the relationship between cannabis use and the development of psychotic disorders is complex and causality is still questioned (Ksir & Hart, 2016a). Although there is now experimental evidence that THC induces psychotic-like symptoms in those without a mental illness (Sagnik Bhattacharyya et al., 2009; V. H. Curran et al., 2002; Englund et al., 2015) and exacerbate symptoms in those with a pre-existing psychotic disorder (D'Souza et al., 2005; Henquet et al., 2010), this does not necessary implicate that those effects lead to the development of a psychosis disorder. Sceptics that question the causal nature of the association between cannabis use and the development of psychosis have proposed several alternative explanations for this association, including:

(1) The link is non-specific, such as any (psychoactive) substance would lead to an increased risk of psychosis. For instance, cigarette use has now been linked to

the development of psychotic disorders (Gurillo et al., 2015) and separating these two substances (tobacco - cannabis) in prediction models can be challenging since most cannabis users are also cigarette smokers and/or consume cannabis mixed with tobacco (Feeney, 2015). So far evidence with regard to the causal effects of cigarette use is considered as too weak to draw more definite conclusions (Alderson & Lawrie, 2015), partly because there is no research to date on whether the effect persist beyond a "shared-vulnerability" to both cigarette use and psychosis (Alderson & Lawrie, 2015; Suzanne H. Gage & Munafò, 2015). Little evidence is in support of alcohol use as a predictor for onset of psychosis when controlled for cannabis use (Galvez-Buccollini et al., 2012). Other lines of research have looked at the link between psychotic symptoms and different illicit substances in separation. To illustrate, studies have reported increased risk of developing psychotic symptomatology in relation to methamphetamine use (McKetin, Lubman, Baker, Dawe, & Ali, 2013) and cocaine use (B. D. Power et al., 2014; Vorspan et al., 2012). Nevertheless, when looked at the effects of multiple substances in separation in a sample of polystimulant dependent users, it was reported that frequency of cannabis use in the last month had the strongest association with positive symptoms severity, followed by frequency of methamphetamine use (Willi et al., 2016). Similarly, in stimulant users, a history of CUD was linked to risk of transient psychotic symptoms in cocaine abusers (cocaine-induced psychosis, CID) (Roncero et al., 2013). It was also reported that age of onset of cannabis use predicted CID in cocaine abusers (Kalayasiri et al., 2010; Trape, Charles-Nicolas, Jehel, & Lacoste, 2014) and increases in cannabis use over time significantly increased the risk for the emergence of psychotic symptoms in chronic methamphetamine

user (McKetin et al., 2013). Finally, it was reported that frequency of cannabis use in the last month but not frequency of cocaine, opioid and alcohol use in the last month was significantly linked to positive symptomatology in polystimulant users (Willi et al., 2016). Together those results may indicate some specificity related to cannabis, i.e. cannabis as a substance that induces psychotic symptoms (even in polysubstance users). Furthermore, when controlled for tobacco, alcohol and other drug use, heavy use of high-potency cannabis remained a significant and strong predictor for onset of psychosis (Di Forti, Marconi, et al., 2015), indicating that those substances did not (fully) mediate the effects of cannabis use. Other independent studies that controlled for comorbid illicit drug use and cigarette use are in further support of an association between cannabis use and risk of psychosis (David M Fergusson et al., 2005; Henquet et al., 2004; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002)

(2) The association between cannabis and psychosis is the results of "self-medication", i.e. those who are mentally less well are more likely to use the substance in order to relieve their symptoms (Khantzian, 1985). For instance, it has been suggested that the emergence of psychotic symptoms in the context of cannabis use may be associated with a pre-existing (genetic) vulnerability for psychosis (McGuire et al., 1995). Some longitudinal studies have addressed this issue by temporal sequencing of the variables of interest (Henquet et al., 2004; Kuepper et al., 2011b), i.e. assessing subsequent development of psychosis following the onset of cannabis use. Furthermore, when adjusting for pre-existing psychotic symptoms, cannabis use was still a significant predictor for subsequent psychotic symptomatology (David M Fergusson et al., 2005; Henquet et al., 2004; J. McGrath et al., 2010). However, those studies do not

fully address the question as to whether the association may be a result of reverse causation (i.e., psychosis risk leading to cannabis use). Studies examining the issue of reverse causation support either a bi-directional relationship (Ferdinand et al., 2005) or a unidirectional risk-effect (David M Fergusson et al., 2005; Henquet et al., 2004; Henquet et al., 2010; Kuepper et al., 2011b; Hélène Verdoux, Gindre, Sorbara, Tournier, & Swendsen, 2003) from cannabis use to risk of development of psychosis. Hence, there is no clear evidence in support of an increase in cannabis use as a result of self-medication that could explain the association found in cross-sectional studies. Using a more short-term temporal analysis by employing the experience sampling method (ESM), it was reported that cannabis use in healthy subjects was linked to subsequent increase in psychotic symptoms (Henquet et al., 2010), but that this effect was only present during the intoxication status and did not remain beyond a 3h interval (Hélène Verdoux et al., 2003). Furthermore, the emergence of psychotic symptoms were not linked to a subsequent increase in cannabis use (Henquet et al., 2010; Hélène Verdoux et al., 2003), which adds to the body of evidence that opposes the notion of self-medication, at least during the acute phase of symptoms.

(3) The link between cannabis use and psychosis is due to uncontrolled sources of confounding. For instance, the first longitudinal study on this topic (Andréasson et al., 1987) was criticized since the important confounding factors were not considered in their analysis. However, re-analysing this data revealed that the effect of cannabis use on risk of developing schizophrenia – which was present in a dose-dependent manner – could not be explained by the inclusion of the confounders defined as other drug use, cigarette and alcohol use, as well as

personality traits (Zammit et al., 2002). Besides, the most recent debate is concerned with the "shared-vulnerability" hypothesis, which proposed that the association reflects the result of a (genetic) liability for both cannabis use and the risk of developing psychosis. To illustrate, it has been proposed that some individuals have and increased susceptibility for generally "problem behavior", including cannabis use, psychosis and other mental health conditions (Ksir & Hart, 2016a). For instance, a meta-analysis reported that the proportion of variance accounted for by genes for (i) initiation of cannabis use and (ii) problematic cannabis use was (i) 48%/40% (males/females) and (ii) 51%/59% (males/females) and there was evidence of a genetic overlap between cannabis initiation and problematic use of cannabis (Verweij et al., 2010), indicating that the genetic vulnerability to continue using cannabis partly overlaps with the genetic vulnerability to initiate cannabis. The question of interest from a "shared-vulnerability" point of view is now whether such genetic vulnerability also overlaps with the vulnerability for psychosis, which has been explored in only a few studies to date. For instance, one study showed that a small proportion of frequency of cannabis use in the general population was explained by the polygenic risk score for schizophrenia (R. A. Power et al., 2014). Similarly, it was reported that a higher morbid risk of schizophrenia was present in relatives of patients who use cannabis when compared to patients who did not use cannabis (McGuire et al., 1995). If cannabis had a unique contribution, one would also expect a higher risk of having a family history of schizophrenia in those not using cannabis prior to the onset when compared to those who were using the substance, which was not the case in the report by J. Boydell et al. (2007). Finally, a higher familial risk for psychosis was present in cannabis

using subjects who developed subsequent psychosis when compared to cannabis using subjects who did not develop psychosis, indicating that cannabis alone may not increase the risk for psychosis without the genetic component (Proal, Fleming, Galvez-Buccollini, & DeLisi, 2014). In sum, although this evidence may indicate that there is some shared genetic vulnerability between cannabis use and schizophrenia, those studies do not allow to draw conclusions as to whether the effect of cannabis on psychosis can be fully explained by such a contribution and some evidence is rather opposed to the hypothesis of a fully genetically confounded association. For instance, one study compared GWAS data concerning cannabis use with GWAS data on 5 different psychiatric disorders; they found a very small overlap with depression but none with schizophrenia (Sherva et al., 2016a). Similarly, Di Forti, Vassos, et al. (2015) reported that cannabis using FEP patients did not significantly differ in they polygenic risk score for psychosis when compared to non-users. Finally, a longitudinal study found an increased risk for the development of schizophrenia that was significantly linked to frequency of premorbid cannabis use when family history of schizophrenia was taken into account (Andréasson, Allebeck, & Rydberg, 1989). Taking this line of evidence into consideration, it seems more plausible that – if any shared genetic vulnerability exists – it would explain only a small proportion of the cannabis-psychosis association. Nevertheless, in order to properly address issues of confounding (including genetic and environmental), it has been suggested that an "*unequivocal proof of cannabis exposure causing psychosis would require the experimental manipulation of cannabis use, with other confounding factors controlled for by random assignment of participants to different groups*" [cf. Ksir and Hart (2016a), Page

3, Paragraph 4], i.e. a placebo-controlled, randomised clinical trial (RCT) involving experimental cannabis administration, which is not feasible in FEP patients for of ethical reasons. Nevertheless, a quasi-experimental approach involving the assessment of within-individual changes in cannabis use over time has been proposed as a compelling alternative, an approach that is considered only second best to RCT when examining causality (J. Murray, Farrington, & Eisner, 2009). The application of such a design, also called fixed-effects analysis of longitudinal panel data (McKetin et al., 2013; Schoeler, Monk, et al., 2016), would allow the adjustment of unobserved time-invariant confounding factors such as shared genetic and environmental factors that do not change over time as well as those observed potential confounding factors that change over time. This model is comparable to the method of the sibling-pair design, in which identical twins discordant for cannabis use are matched in unmeasured time-invariant factors including genetic and environmental factors. When employing such analysis, David M Fergusson et al. (2005) reported that the effect on risk of psychotic symptoms remained significant, which does not support the hypothesis that the association arose due to a shared a genetic vulnerability, consistent with independent evidence in chronic methamphetamine users without a comorbid diagnosis of psychosis, in whom change in frequency of cannabis use was linked to the risk of presence of psychotic symptoms (McKetin et al., 2013). This is also in accordance with a study that employed a sibling-pair design to control for some of the shared genetic (<50%) and environmental influence by J. McGrath et al. (2010), which found that duration of cannabis use was a significant predictor of psychotic outcome in young adults. Those studies (David M Fergusson et al., 2005; J. McGrath et al., 2010; McKetin et al., 2013)

are also suggestive of a dose-response relationship between frequency of cannabis use and psychotic symptoms when controlling for pre-exposure confounding factors, an important criteria when establishing causality (A. B. Hill, 1965). In accordance, there is evidence that reported an increased risk for subsequent psychosis linked to cannabis frequency when controlled for other factors that indicate risk taking behavior/addictive traits (other drug use, alcohol use, cigarette use) (Zammit et al., 2002). Therefore the accumulated evidence is in favour of cannabis as a contribution factor for psychosis, even if genetic influences such as "shared-vulnerability" are taken into consideration.

To summarise, although there are still scepticisms questioning a causal relationship between cannabis use and risk of psychosis (Ksir & Hart, 2016a) and patients with psychosis often do not believe that cannabis is a causal factor linked to their illness (Buadze, Stohler, Schulze, Schaub, & Liebrenz, 2010), there is nevertheless good-quality evidence to believe that cannabis use is a causal risk factor for the development of psychotic disorders (Robin M. Murray & Di Forti, 2016). Nevertheless, it has been concluded that cannabis is not a sufficient cause for psychosis but rather constitute a component cause (Henquet et al., 2004), interacting with other factors such as family history of psychosis, genetic factors, childhood trauma/abuse and age of onset of use (Radhakrishnan, Wilkinson, & D'Souza, 2015).

2.5.3 SUMMARY

Chapter 2 has shown that cannabis is a complex plant and extracts of the plant contain a range of chemicals that affect human behaviour in different ways. Although longitudinal evidence regarding the effects of cannabis use and the risk of development of psychiatric disorders has accumulated over the last decade, this topic is still a matter

of debate. There is now evidence supporting a link between cannabis use and the risk of poor mental health outcomes, such as the development of psychosis (Di Forti, Marconi, et al., 2015; David M Fergusson et al., 2005; Marconi et al., 2016; T. H. Moore et al., 2007), depression (Schoeler et al., under review), anxiety (Whiteford et al., 2013), bipolar disorder (Lagerberg et al., 2011; Van Laar et al., 2007), cognitive impairments (Meier et al., 2012; Schoeler et al., 2015) and substance use disorders (SUD) (Blanco et al., 2016). While the results are largely consistent with regard to conditions such as psychosis and SUD, there is evidence that does not support a link between cannabis and other outcomes, such as depression (Blanco et al., 2016; Danielsson et al., 2016; Whiteford et al., 2013), anxiety (Blanco et al., 2016; Danielsson et al., 2016), changes in cognition (N. J. Jackson et al., 2016) and bipolar disorder (Blanco et al., 2016). Discrepancies across studies perhaps relate to the different methodologies employed and the limitations inherent to them, such as the use of cross-sectional designs, insufficient power to detect significant effects, the non-consideration of important confounders, the lack of exploration of dose-response patterns, a focus on varying age ranges or differences in geographic locations, which makes it difficult to derive at a more confident conclusion regarding the effects of cannabis use mental health conditions. Furthermore, different outcomes of interest (in this case mental health conditions) require the implementation of different methodological considerations. For instance, period of abstinence from cannabis is a crucial factor when assessing the non-acute effect of cannabis on cognitive outcome, while close monitoring of early patterns of cannabis use is particularly important for conditions that usually manifest early in life such as psychotic disorders. The application of a life-span approach would be particularly important when looking at behavioral changes that are more likely to occur later in life such as depressive disorders. Finally, once a (causal) risk factor is identified,

it needs to be evaluated whether its impact is of relevance for policy makers, i.e. whether efforts for prevention would actually lead to noticeable changes in terms of personal costs (e.g. preventing mental health problems, improving cognition) and economic costs (e.g. decreased hospital costs, reduced loss in productivity due to improvements in employment status).

2.6 CONTINUED CANNABIS USE IN PATIENTS WITH PRE-EXISTING PSYCHOSIS

2.6.1 INTRODUCTION

Cannabis use and the presence of cannabis use disorders (CUD) are common in patients with a first episode psychosis. Varying rates of comorbidity have been reported, depending on the specific definition of cannabis use. For instance, as shown in *Figure 8*., the presence of lifetime (light) cannabis use was reported by an average of 58% (range 20%-89%) of patients at onset of the illness, while a history of heavy lifetime use prior to the onset was reported by about 32% (19%-50% range). The prevalence rates of patients who reported current use at onset come to estimates of about 39% (10%-56%) for current (light) cannabis use and 30% (10%-55% range) for current heavy cannabis use (cf. *Figure 9*.). Those rates are much higher when compared to estimates from the general population for annual use in young adults (~12%) in Europe (EMCDDA, 2015). A meta-analysis found that 44% of FEP patients present with a lifetime cannabis use disorder (CUD) and 29% with a current CUD (Johanna Koskinen, Löhönen, Koponen, Isohanni, & Miettunen, 2010), whereas the general population rates are usually around 10% for lifetime CUD (Haberstick et al., 2014) and about 3% in those aged 14-17 (Wittchen et al., 2007). In a separate meta-analysis, the pooled prevalence rate of cannabis use present at onset (presence of CUD or at least monthly use) was identified as 35% (35 samples, 95% Confidence Interval = [31%-39%]) (Myles, Myles, & Large, 2015). This is in line with case-control studies that reported much higher rates of current cannabis use in patients with an FEP when compared to healthy controls [30% vs. 11% for current use (at least daily)] (Di Forti, Marconi, et al., 2015) and when compared to controls with non-psychotic mental illness [38% vs. 17% for current use (any use in the 3 months prior onset)] (Paruk, Jhazbhay, Singh, Sartorius, & Burns, 2016), although

those groups did not differ with regard to lifetime history of cannabis use (Di Forti, Marconi, et al., 2015; Paruk et al., 2016). In contrast, rates for other substances including tobacco and alcohol are not always higher in FEP patients and when compared to non-psychotic controls with mental illness (Paruk et al., 2016) and FEP patients did not differ from healthy controls with regard to alcohol consumption and use of other illicit drugs (Di Forti et al., 2012). Those mainly self-report based prevalence rates for cannabis use at onset are likely to be representative estimates, considering that results from urine drug screens usually have high concordance with data from self-reports (Baeza et al., 2009; Batalla et al., 2013b; Di Forti et al., 2012). Other evidence suggests that the rates of cannabis use in FEP patients may have risen over time. For instance, in London the prevalence of cannabis use (any use in the year prior to the presentation) in first episode psychosis individuals (first presentation schizophrenia) was found to be about 5% in the 1960th and has risen to 50% in the 1990th (J Boydell et al., 2006). This increase in prevalence was not found in patients with other non-psychotic psychiatric disorders from the same area (J Boydell et al., 2006). When compared to other SUDs, CUD has been reported to be the most commonly SUD diagnosed at onset (17%), followed by AUD (alcohol use disorder) (11%) and stimulant use disorder (2%) in FEP patients (Cantwell et al., 1999), which is similar to the rates that were reported at onset of illness in another FEP cohort (e.g. 14% CUD only, 10% AUD only, 3% other SUD) (Van Mastrigt et al., 2004). Similarly, in ultra-high-risk individuals, cannabis is the most commonly used and abused drug, with higher prevalence when compared to other illicit drugs (Valmaggia et al., 2014) and rates of abuse that are higher when compared to alcohol (Auther et al., 2015). FEP patients may also differ from the general population with regard to their preferred type, since it was found that patients were more likely to use high-potency forms of cannabis (skunk-type)

than healthy controls (53% vs. 19%) and less likely to use milder forms (hash-type) (14% vs. 44%) (Di Forti, Marconi, et al., 2015). From these estimates it is clear that cannabis is a commonly used drug of abuse in those presenting with their first episode of psychosis. However, with regard to the effects of cannabis use on outcome in FEP, the crucial question is whether cannabis use remains a prevalent problem following onset of psychosis, i.e. whether those who are users at onset continue to use the substance or whether non-users at onset start using the substance following the onset. Frist, cannabis remained the most prevalent drug of use when assessed at follow up (Lange et al., 2014). In fact, all FEP subjects that with a diagnosis of SUD at follow up reported to be cannabis abusers (Levy et al., 2012). Similarly, D Wade et al. (2006) reported that CUD was most common (42%) at follow up, followed by AUD (30%) and stimulant use disorder (17%) (D Wade et al., 2006). This is consistent with reports from patients with established schizophrenia, in which the most prevalent use disorder was found to be CUD (11%), followed by stimulant use disorder (9%) and opioids use disorder (4%) (Kivimies et al., 2016). Encouragingly, there is a relatively high proportion of patients who stop using the substance following the onset. For instance, studies reported that there is a significant decrease in the prevalence of cannabis use between onset and the first year of follow up (Baeza et al., 2009; Hinton et al., 2007; Seddon et al., 2015). In line with this, a recent meta-analysis reported that patients with FEP significantly reduced cannabis intake (number of days used) between onset and follow up (Rebgetz, Kavanagh, & Hides). As illustrated in *Figure 9.* below., between 24% and 66% (mean of 46%) of those with baseline cannabis use decrease or stop using the substance. Moreover, the rate of those who start following the onset is relatively low, ranging between 0% and 33% (mean of 11%). On the other hand, there is a large proportion of patients who continue using the substance, with an overall estimate of

46% found here (range 26% - 63%, cf. *Figure 9.*). The results implicate that data on premorbid (lifetime cannabis use) or cannabis use at onset may not be valid measures for risk on outcome, since the course of cannabis use varies greatly following the onset. However, one limitation inherent to these follow up studies potentially lies in their way of classifying cannabis users into continuers, discontinuers, starters and non-users, which has been done mainly based on relatively crude approximations (cf. *Table 9.* below).

Figure 8. Cannabis use prevalence at onset of psychosis[1]

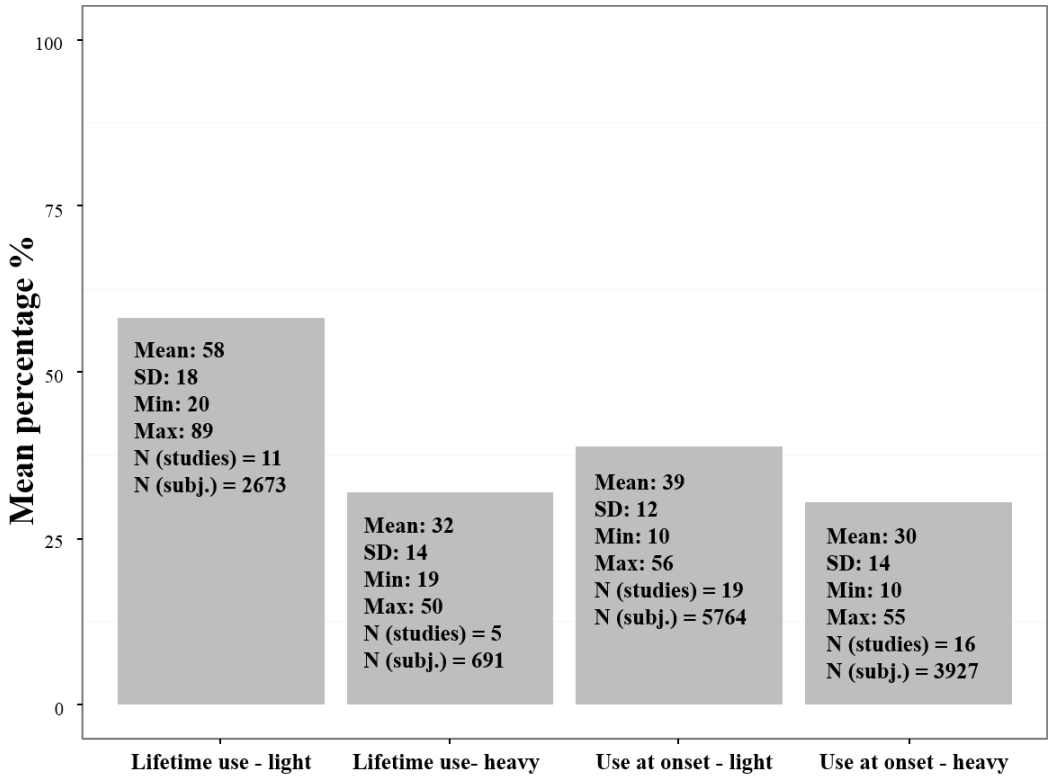
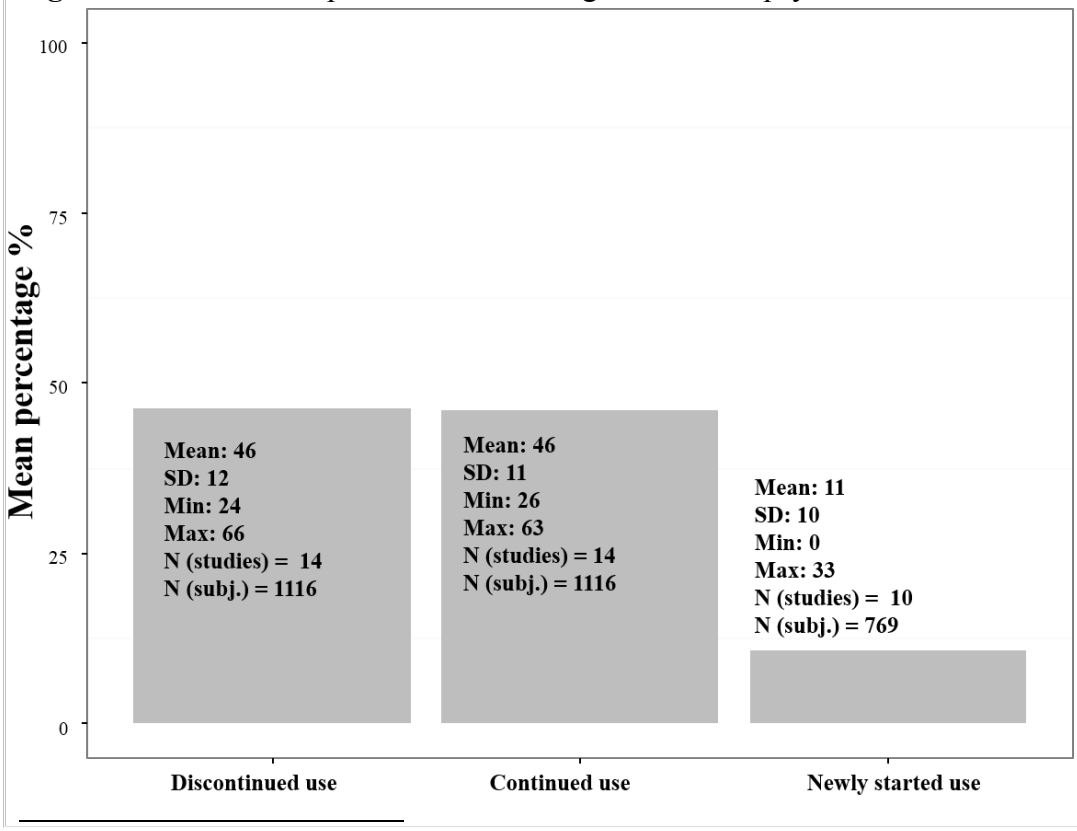


Figure 9. Cannabis use prevalence following the onset of psychosis[1]



[1] **Note.** Summary of prevalence rates reported by studies in FEP patients (cf. *aTable 3.*and *aTable 4.* for references, Appendix III)

Table 9. Cannabis use profiles in follow up studies in FEP patients

Study	Non-user	Discontinuer	Continuer	Starter
B. Schimmelmann et al. (2012)	Absence CUD at BL and FU	Presence CUD at BL, decrease in quantity ≥50% at FU	Presence CUD at BL and no change in quantity of increase (>50%) at FU	Absence of CUD at BL and presence of CUD at FU
Seddon et al. (2015)	No use reported at BL and FU	Use (≥1) 3 months prior BL but not 3 months prior FU	Use (≥1) 3 months prior BL but and use 3 months prior FU	No use (<1) 3 months prior BL but and use (≥1) 3 months prior FU
J. Stone et al. (2014)	No use (<1) reported at BL and FU	Reduced use at FU than BL	Use (≥1) reported at BL and FU	-
L. Clausen et al. (2014)	No use (<1) one year prior BL and one year prior FU	Use (≥1) one year prior BL, no use (<1) one year prior FU	Use (≥1) one year prior BL, use (≥1) one year prior FU	No use (<1) one year prior BL, use (≥1) one year prior FU
Faber et al. (2012)	No use (>1) at onset and FU	Use (>1) at onset, discontinued subsequently	Use (>1) at onset, continued subsequently	-
Faridi, Joober, and Malla (2012)	Absence CUD at BL and FU	Presence CUD at BL, absence CUD FU	Presence CUD at BL, absence CUD FU	Absence CUD at BL, presence CUD FU
González-Pinto et al. (2011)	No use (< 4) in year before onset, no use (< 4) in year before FU	Use (≥ 4) in year before onset, no use (< 4) in year before FU	Use (≥ 4) in year before onset, use (≥ 4) in year before FU	No use (< 4) in year before onset, use (≥ 4) in year before FU
Miller et al. (2009)	Absence CUD at BL no use (<1) throughout FU	Presence CUD at BL, no use (<1) throughout FU	Presence CUD at BL, use (≥1) throughout FU	Absence CUD at BL, use (≥1) throughout FU
Anton Grech, Jim Van Os, Peter B. Jones, Shon W. Lewis, and Robin M. Murray (2005a)	No history of (regular/frequent) use at BL, no use (<1) in 3 months prior FU	History of (regular/frequent) use at BL, no use (<1) in 3 months prior FU	History of (regular/frequent) use at BL, use (≥1) in 3 months prior FU	No history of (regular/frequent) use at BL, use (≥1) in 3 months prior FU
Barbeito et al. (2013)	No use (<1) at BL and FU	Use (≥1) at BL and no use (<1) FU	Use (≥1) at BL and use (≥1) FU	No use (<1) at BL and use (≥1) FU
Hinton et al. (2007)	No use (<1) in 1 month prior BL, no use at FU	Use (≥1) in 1 month prior BL, no use at FU	Use (≥1) in 1 month prior BL, use at FU	No use (<1) in 1 month prior BL, use at FU
Baeza et al. (2009)	No use (<1) in 1 month prior onset, no use (<1) in 1 month prior FU	Use (≥1) in 1 month prior onset, no use (<1) in 1 month prior FU	Use (≥1) in 1 month prior onset, use (≥1) in 1 month prior FU	No use (<1) in 1 month prior onset, use (≥1) in 1 month prior FU

Note. BL = Baseline assessment; CUD = Cannabis use disorder; FU = Follow up assessment.

When presenting with a first episode psychosis, cannabis-using patients have been shown to be different from non-using patients in a range of variables. For instance, cannabis-using FEP patients were characterised by a younger age of onset (Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006; Clausen et al., 2013; Di Forti, Marconi, et al., 2015; Foti, Kotov, Guey, & Bromet, 2010; González-Pinto et al., 2011; Patel R et al., 2016; Seddon et al., 2015; Stirling, Lewis, Hopkins, & White, 2005; Van Mastrigt et al., 2004), higher uses of other illicit drugs (Gonzalez-Blanch et al., 2015), more severe psychotic symptoms (Baeza et al., 2009; Seddon et al., 2015; Stirling et al., 2005), as well as reduced insight into the illness (B. G. Schimmelmann et al., 2012). These correlates are similar to those that were linked to continued cannabis use following the onset. For instance, continued cannabis use was linked to higher uses of alcohol (González-Pinto et al., 2011) and other illicit drug use (González-Pinto et al., 2011), younger age of onset (L. Clausen et al., 2014; González-Pinto et al., 2011), higher premorbid IQ (L. Clausen et al., 2014), medication non-adherence (L. Clausen et al., 2014; Foglia et al., 2017). Therefore, those factors are important to consider in prediction models looking at the effect of continued cannabis use in patients with psychosis, since they may confound the association between cannabis use and outcome.

2.6.2 Continued cannabis use in first episode psychosis: Clinical and functional outcome

Numerous studies have looked at levels of symptoms severity by comparing cannabis using patients to non-using controls. When assessed at onset, the evidence is rather mixed, reporting either increased positive symptoms in cannabis using patients when compared to non-users (Baeza et al., 2009; Seddon et al., 2015; Stirling et al., 2005), although there are several studies that did not find differences between the two

groups in terms of positive symptoms (Compton, Furman, & Kaslow, 2004; Gonzalez-Blanch et al., 2015; González-Pinto et al., 2011; Hinton et al., 2007; Van Mastrigt et al., 2004). Findings are more consistent if studies investigated the effect of different patterns of cannabis use following the onset, such as continuation and discontinuation of cannabis use. For instance, in my meta-analysis (Schoeler, Monk, et al., 2016), I found that continued use was linked to higher positive symptoms, while no such effect was present in those who discontinued using cannabis following the onset. Other FEP studies have reported that continued cannabis use was linked to an increase in symptoms from onset to follow up (Foti et al., 2010; Rais et al., 2008; Seddon et al., 2015). Continued cannabis use was also linked to higher risk of non-remission at follow up when compared to non-users (B. Schimmelmann et al., 2012). Those who discontinue or reduced their cannabis intake following the onset appeared to have the best outcome in terms remission status (B. Schimmelmann et al., 2012).

Unlike the more robust findings on positive symptomatology in the context of ongoing cannabis use, the association between level of functioning over the course of the illness, as well as the severity of negative symptomatology in the context of cannabis use has not yet been well established. When assessed at onset, cannabis using patients are generally not significantly different from non-using patients in their level of functioning (L. Clausen et al., 2014; Gonzalez-Blanch et al., 2015; González-Pinto et al., 2011; Hinton et al., 2007). This is also in accordance with reports of no significant differences in premorbid adjustment between cannabis users and non-users in FEP patients (Baeza et al., 2009; Elkins, 2004; Stirling et al., 2003; Van Mastrigt et al., 2004). Similarly, with regard to negative symptoms, studies that assessed FEP patients at onset have reported that cannabis users were characterised by fewer negative symptoms (Baeza et al., 2009; Compton et al., 2004), although other studies did not find

differences in negative symptomatology between users and non-users in FEP patients at onset (Gonzalez-Blanch et al., 2015; González-Pinto et al., 2011; Hinton et al., 2007; Seddon et al., 2015; Stirling et al., 2005). Overall, there is no consistent evidence that cannabis use is linked to higher levels of functioning, including premorbid adjustment and negative symptoms when assessed at onset. This association is perhaps somewhat different over the course of the illness, e.g. frequency of cannabis use assessed at onset of illness has been found to predict level of functioning 10 years later (Bergh et al., 2016). Furthermore, continued cannabis use was linked to lower GAF scores at follow up when compared to non-users (B. Schimmelmann et al., 2012). Interestingly, those FEP patients who discontinued or reduced their cannabis intake following the onset appeared to have the best outcome in terms of functioning (B. Schimmelmann et al., 2012). This was also confirmed in my recently published meta-analysis (Schoeler, Monk, et al., 2016), which showed that patients with psychosis (at all stages of their illness) who continued to use cannabis were not different in their level of functioning, while those discontinued to use cannabis following the onset where characterised by higher levels of functioning when compared to non-users. No effect of discontinuation was present with regard to negative symptom severity at follow up (Schoeler, Monk, et al., 2016). Nevertheless, studies that looked at changes over time reported that discontinued cannabis users had larger improvements in functioning when compared to those continued (González-Pinto et al., 2011; J. Stone et al., 2014), although not all studies are in support of this (Hinton et al., 2007). No differences in changes in symptoms between continuer and discontinuer were present for negative symptoms (González-Pinto et al., 2011; Hinton et al., 2007). Using a longitudinal analysis to estimate the effects of change in cannabis use over time, it was reported that FEP patients were not characterised by higher negative symptoms in periods when they were

using cannabis when compared to periods when they were not using cannabis following the onset (Foti et al., 2010).

With regard to cognitive outcome in psychosis, its relation to continued cannabis use is still poorly understood. In fact, there is an almost consistent paradoxical finding that has been reported by studies investigating this issue; First, when tested at onset, heavy cannabis users (daily use) were characterized by fewer neurological soft signs when compared not non-users (Ruiz-Veguilla et al., 2009) and onset users (any use) performed better in measures for short-term memory (Stirling et al., 2005) , visual memory (Stirling et al., 2005), tests assessing attention and psychomotor speed (Donoghue & Doody, 2012), and performance in reasoning, problem-solving and visual memory (Potvin, Joyal, Pelletier, & Stip, 2008). Similarly, it was reported that premorbid cannabis use significantly predicted better cognitive function at onset (Leeson et al., 2012), and that this effect was explained by higher levels of premorbid function present in cannabis users when compared to non-users (Leeson et al., 2012). With regard to cognitive outcome following the onset, the findings seem equally paradoxical: For instance, cannabis users were not significantly different in tests assessing short-term memory (Power et al., 2015; Sevy et al., 2007) or long-term memory (Sevy et al., 2007) or decision making (Sevy et al., 2007). Furthermore, a recent study found that FEP patients with a history of early onset cannabis use performed better on cognitive measures than those without (Hanna et al., 2016). When pooling together the available evidence in my meta-analysis (Schoeler, Kambeitz, et al., 2016), I found that cannabis using patients performed better in tests assessing memory function when compared to non-users ($d = -0.11$), particularly for the domains of visual immediate recall ($d = -0.73$), verbal recognition ($d = -0.34$) and visual recognition ($d = -0.41$). A recent meta-analysis also reported that psychotic patients with unspecified co-

morbid substance use disorder performed significantly better in tests measuring verbal learning and memory ($d = -0.26$) than those without (Donoghue & Doody, 2012). In this context, it has been proposed that while patients with schizophrenia are thought to have a neurodevelopmental disorder (R. M. Murray & Lewis, 1987), drug abuse may provide an alternative pathway to developing psychosis (Robin M Murray, Paparelli, Morrison, Marconi, & Di Forti, 2013). Such a view would suggest that cannabis using patients with psychosis may represent a subgroup with less neurodevelopmental pathology and less neurocognitive impairment than non-using patients in the first place (Schoeler et al., 2015). Problematically, those studies cited here are cross-sectional in their nature and do not allow to draw conclusions regarding the effects of ongoing cannabis use and cognitive outcome, which should be assessed in terms of cognitive change between onset of illness and follow up. For instance, using a longitudinal assessment, a neuroimaging study reported a loss of cortical thickness linked to cannabis use in the 5 years following the onset, which was reported to be present in areas rich of CB_1 receptors such as ACC and the DLPFC (Rais et al., 2010). This may indicate adverse effects of ongoing cannabis use on cognition, although further studies are necessary that specifically test this hypothesis.

Other follow up studies looked at outcome defined in terms of affective symptoms and anxiety, although evidence on the effect of continued cannabis use in FEP patients is still sparse. For instance, substance abuser (60% cannabis user) where more likely to report suicidal behaviour in 2 years following the onset (H Verdoux et al., 2001). Similarly, FEP subjects with onset cannabis use were more likely to commit a suicide attempt following the onset than non-users (Ayesa-Arriola et al., 2015). A recent review concluded that there is a relatively robust link between suicidal behavior and cannabis use in patients with psychosis (that are at different stages of their illness),

although a summary of the current evidence appears challenging due to the heterogeneous methodological designs employed by the studies (Serafini et al., 2012). Other studies reported that patient who continued to use cannabis (use at baseline and follow up) were more severely depressed than non-users at follow up (Seddon et al., 2015; J. Stone et al., 2014). However, other reports do not support the link between continued cannabis use and depression when assessed at follow up (Baeza et al., 2009; Hinton et al., 2007). More conclusive evidence comes from studies that assessed changes in depression severity over time. For instance, in a longitudinal study using fixed effects analysis that allowed to control for time-invariant sources of (environmental and genetic) confounding, change in cannabis use in FEP patients was not linked to changes in depression severity (Foti et al., 2010). Similarly, Degenhardt et al. (2007) reported that changes in cannabis use were not significantly linked to changes in depressive symptoms, which were only predicted by level of prior depressive and psychotic symptoms and prior use of amphetamines in a sample with established schizophrenia. Similarly, when testing the reverse direction, changes in cannabis use were not preceded by change in depressive symptoms (Degenhardt et al., 2007). In fact, when comparing patients with psychosis (at all stages of psychosis) in my meta-analysis, I found that cannabis using patients were less depressed than those who were considered as non-users (Schoeler, Kambeitz, et al., 2016). Overall, while there is some (although conflicting) evidence suggestive of cannabis use as a potential risk factor for later life affective symptoms and anxiety in the general population (cf. **Chapter 2.5** above), so far the evidence regarding the effects of cannabis use on depressive symptoms in young patients with a first episode psychosis is not indicative of changes in depressive symptoms following cannabis use. Nevertheless, future follow up studies

using longer follow up durations when investigating changes in depression severity are needed in this context to draw more confident conclusions.

Finally, an important factor to outline in this section is the issue of medication non-adherence in patients with psychosis, which is considered as a major problem in the treatment of patients with psychosis. For instance, estimates from systematic reviews indicate that an average of 26% of patients with established psychosis are not adherent (Nose et al., 2003), although a recent review concluded that rates vary greatly (reported rates between 47% and 95%) across studies (Sendt et al., 2015). Reports from follow up studies in FEP patients indicate a rate of approximately 37% non-adherence in patients followed up within the first two year of the illness, 29% in those followed up between two to five years and about 49% in those followed up for more than five years (cf. *Figure 1.* above). This factor has been consistently linked as a predictor for poor outcome, including risk of relapse and suicide (Higashi et al., 2013; Schoeler, Petros, Di Forti, Klamerus, et al., 2016). Studies investigating adherence to treatment in the context of cannabis use mainly reported that patients who continued using cannabis following the onset were less adherent to their medical treatment plan than their non-using comparisons, as reported by a recent meta-analysis (Foglia et al., 2017). It is therefore plausible that medication non-adherence could act as a mediator between cannabis use and outcome. For instance, it has been reported that non-compliance mediated the relationship between continued cannabis use in the first year following the onset and risk of non-remission in patients with psychosis (Colizzi et al., 2015). In this context, it has been suggested that patients may use cannabis as a form of self-medication to relive their symptoms (Khantzian, 1985) and prefer using the cannabis instead of antipsychotic medication due to the lack of side effects. Nevertheless, it was reported that cannabis use remained a predictor for poor outcome even if patients are

adherent to antipsychotic medication (Faridi et al., 2012; Hides, Dawe, Kavanagh, & Young, 2006; Sorbara, Liraud, Assens, Abalan, & Verdoux, 2003). As one mechanism of action, it has been proposed that cannabis may increase the risk of non-response to antipsychotic medication (Patel R et al., 2016). For instance, onset cannabis use predicted treatment failure (defined as the number of unique antipsychotics prescribed) within the 2 years following the onset (Patel R et al., 2016). In contrast, another observational study reported that onset presence of CUD was not significantly linked to response to antipsychotic medication within the acute phase of the illness (6 weeks from start of treatment) (Crespo-Facorro et al., 2007) and in a 5-year follow up, continued cannabis use was not linked to the cumulative amount of antipsychotic medication prescribed (Rais et al., 2010). However, this is not in line with experimental evidence that showed that haloperidol did not reduce the psychotogenic effects following THC administration (D'Souza et al., 2008). To conclude, there is no clear evidence to date as to whether cannabis is likely to lead to non-response to antipsychotic medication, for which reason further research is warranted to shed light into this question.

2.6.3 SUMMARY

While to date there is good evidence to believe that cannabis plays a causal role in the development of psychotic disorders (Robin M. Murray & Di Forti, 2016), evidence with regard to outcome in first episode psychosis is less clear. Overall, it seems important to distinguish between the different outcomes that have been assessed (functional, symptomatic, cognitive). The evidence appears to be more consistent with regard to symptomatic outcome than functional outcome. For instance, while FEP patients were characterised by more severe positive symptoms in periods in which they used cannabis, no such effects were present for negative symptoms or levels of

depression (Foti et al., 2010). Furthermore, it became obvious that cannabis measures that incorporate the varying course of the cannabis use patterns following the onset are of crucial relevance since those changes may be drivers in the cannabis-outcome association. Taking into account the limitations from the available evidence therefore highlights the importance of using longitudinal assessments of change in outcome (e.g. change in symptoms, relapse following the onset) instead if comparing the groups in outcome measures at follow up in a cross-sectional manner. For instance, while continued cannabis users did not differ from FEP non-users in their negative or positive symptoms at follow up, continued users did in fact show significant less improvements in their symptoms when compared to non-users (Rais et al., 2010). Evaluating the outcome in cannabis using patients is further complicated by the fact that users are likely to differ in many factors – i.e. factors that may confound the relationship- from the non-users, including the more easily assessable demographic characteristics such as age (age of onset), gender, ethnicity, or observable factors that can be measured over time such as medication adherence, other drug use, as well as unmeasured time-invariant factors that may impact on the association such as genetic contributions. Considering that cannabis use is a modifiable factor that is accessible for direct treatment, there is the urgent need to further investigate the role of continued cannabis use following the onset of psychosis since this has the potential to reduce the emotional and economic burdens associated with the event of a relapse.

3 PAPER 1: CONTINUED VERSUS DISCONTINUED CANNABIS USE IN PATIENTS WITH PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 ABSTRACT

Background. Although the link between cannabis use and development of psychosis is well established, less is known about the impact of continued versus discontinued cannabis use after the onset of the illness. No meta-analysis has as yet summarized the evidence focusing on the relationship between continued and discontinued cannabis use following onset of psychosis and its relapse.

Methods. Studies were identified through a systematic literature search. Relapse outcomes were compared between those who continued (CC) or discontinued (DC) cannabis use or were non-users (NC). Cohen's *d* was estimated and entered into Random Effects Models (REM) to compare (1) CC-NC, (2) CC-DC and (3) DC-NC. Meta-regression and sensitivity analysis were employed to address the issue of heterogeneity.

Findings. Twenty-four studies (N=16565) were included. Independent of the stage of illness, continued cannabis users had significantly ($p \leq 0.05$) worse relapse outcome than both non-users ($d_{CC\text{-}NC}=0.36$) and discontinued users ($d_{CC\text{-}DC}=0.28$), as well as longer hospitalisations ($d_{CC\text{-}NC}=0.32$). In contrast, cannabis discontinuation was not associated with relapse ($d_{DC\text{-}NC}=0.02$, $p=0.82$). Meta-regression indicated greater effects of continued compared to discontinued cannabis use ($p \leq 0.05$) on relapse, positive symptoms and level of functioning but not negative symptoms.

Interpretation. Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospitalisations and more severe positive symptoms - adverse effects that are absent in those who discontinue use of

cannabis. These findings point to reductions in cannabis use as a crucial interventional target to improve outcome in patients with psychosis.

3.2 INTRODUCTION

Cannabis is the most commonly used illicit drug in patients with an existing psychotic disorder (Barrowclough, Emsley, Eisner, Beardmore, & Wykes, 2013). In some studies about one out of every four patients with psychosis meet the criteria for cannabis dependence (J. Addington & Addington, 2007; J. Koskinen, Lohonen, Koponen, Isohanni, & Miettunen, 2010) with rates of use especially high in young people presenting with their first psychotic episode (J. Koskinen et al., 2010). These rates are much higher than those of the general population (Regier et al., 1990) or those with other psychiatric diagnoses (Agosti, Nunes, & Levin, 2002b). While the association between cannabis use and onset of psychotic disorders is well-established (Arseneault, Cannon, Witton, & Murray, 2004; Stepniak et al., 2014), suggesting that cannabis use is a component cause of the disorder (Di Forti, Marconi, et al., 2015), its effect on the course of psychosis following onset is less clear. This lack of clarity seems mainly related to limitations of study design such as cross-sectional approach, underpowered samples and lack of consideration of potential confounders [reviewed here (Zammit et al., 2008b)]. However, more recent studies implicate cannabis use as a potential risk factor for relapse of psychosis as indexed by readmission to hospital (San, Bernardo, Gómez, & Peña, 2013b; Sorbara et al., 2003; D. van Dijk, M. W. J. Koeter, R. Hijman, R. S. Kahn, & W. van Den Brink, 2012c), with some evidence supporting a dose-response relationship (Hides et al., 2006). Other studies reported worsening of positive psychotic symptoms (Foti et al., 2010; Anton Grech, Jim Van Os, Peter B Jones, Shon W Lewis, & Robin M Murray, 2005b) or shorter time to symptom re-emergence (Linszen, Dingemans, & Lenior, 1994) in cannabis-using patients with psychosis. These findings are in line with experimental pharmacological challenge studies reporting that delta-9-tetrahydrocannabinol (THC), the main psychoactive

constituent in cannabis, can induce transient psychotic experiences in healthy individuals and worsen existing symptoms in patients with pre-existing psychosis (S. Bhattacharyya, Z. Atakan, et al., 2012; S. Bhattacharyya et al., 2009; Cortes-Briones et al., 2015; D'Souza et al., 2005).

If cannabis use were really associated with worse outcome in those with established psychosis, then one would expect that those who continue using cannabis would have far worse outcome compared to those who stop. However, while some evidence suggests that discontinuation of cannabis use may lead to a reduction in readmission rates (González-Pinto et al., 2009; van der Meer & Velthorst, 2015) and improvement in symptomatic and functional outcome of psychosis (Baeza et al., 2009; Clausen et al., 2013; Grech et al., 2005b; B. G. Schimmelmann et al., 2012; J. M. Stone et al., 2014; van der Meer & Velthorst, 2015), others suggest that this may not necessarily be the case (Barrowclough et al., 2013; Faber et al., 2012; van Dijk et al., 2012c). Although about 30-50% of cannabis users stop using it after the onset of their psychotic illness (González-Pinto et al., 2009; Grech et al., 2005b; I. Harrison et al., 2008b; J. M. Stone et al., 2014; van der Meer & Velthorst, 2015), suggesting that this may be a clinically relevant issue worth exploring, there is lack of clarity in terms of existing evidence as outlined earlier. Furthermore, conclusions from the individual studies need to be treated with caution in light of the relatively modest sample sizes. Meta-analytic techniques offer a method of overcoming the sample size issue by statistically integrating the results from a number of separate studies thereby improving the power to detect significant effects (Kambeitz et al., 2012). Considering the conflicting evidence from individual studies investigating the relationship between continued cannabis use and relapse and from studies looking at discontinued use and outcome, I have attempted to quantitatively summarize the current evidence. In this

study, I aimed to (a) establish whether ongoing cannabis use is associated with poor outcome in established psychosis and (b) establish the magnitude of this effect by pooling together the results of all available studies using a meta-analytic approach. In particular, I focused on outcome defined as 'relapse of psychosis', operationalized as either readmission to hospital or based on investigator-determined psychotic relapse. Since cannabis use is potentially amenable to treatment and given that a substantial proportion of patients with psychosis continue using the drug following onset of their illness, there is a particular need to estimate the effect of ongoing cannabis use on a robust measure of outcome which is indicative of relapse, such as hospitalisation. This is a reliably estimated measure, with significant implications for the cost of healthcare (Knapp et al., 2014). Although previous meta-analyses have investigated the association between continued and discontinued cannabis use and outcome in psychosis, these have mainly focused on symptomatic outcome measures such as positive and negative symptoms or depression scores, while outcome indexed by hospitalisation was only considered in the context of the effects of substance use in general (Gupta, Mullin, Nielssen, Harris, & Large, 2013; Large, Mullin, Gupta, Harris, & Nielssen, 2014; Mullin et al., 2012b). I therefore set out to investigate whether (i) continued use of cannabis following the onset of psychosis is associated with worse relapse outcome relative to non-users, (ii) discontinued use of cannabis subsequent to the onset of psychosis is associated with a worse relapse outcome comparable to non-users and (iii) discontinued use of cannabis is associated with a better relapse outcome compared to continued use. Furthermore, I investigated whether the effect of cannabis use on outcome was consistent across different outcome measures by also examining effect on measures such as length of hospitalisation, symptom severity and level of functioning.

3.3 METHODS

3.3.1 STUDY SELECTION

A systematic search strategy was used to identify all relevant studies, following the methods recommended by the Cochrane Handbook (J. P. Higgins, Green, & Collaboration, 2008) and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Beller et al., 2013). Firstly, the MEDLINE database was searched for English language studies using a combination of search terms describing the cannabis terms (marijuana/marihuana, cannabis, illicit, substance), the outcome of interest (outcome, hospital*, relapse, readmission) and the study population (psycho*, bipolar, schizophrenia), with the final search conducted on the 21st of April 2015. Following this, bibliographies of the identified publications and previous published meta-analyses were hand-searched in order to identify additional studies that met the inclusion criteria but might have been missed by the database search. Studies were selected if they included a sample of patients with a pre-existing psychotic disorder (schizophrenia, schizoaffective, bipolar if outcome was reported as number of psychotic episodes [e.g. Ringen et al. (2010)]), with a follow-up duration of at least 6 months. The primary predictor variables were defined as (1) continued cannabis use (yes/no) after onset of illness and (2) discontinued cannabis use after onset (yes/no). Only a subset of the total pool of studies that examined the effect of continued cannabis use on outcome also examined the effect of discontinuation of the drug. I excluded studies if 'continued cannabis use' (CC)/ 'discontinued cannabis use' (DC) could not be established, e.g. studies that assessed cannabis use only around the onset of illness (Basu, Malhotra, Bhagat, & Varma, 1999; Batalla et al., 2013a; Manrique-Garcia et al., 2014a; Grant E Sara, Philip M Burgess, Gin S Malhi, Harvey A Whiteford, & Wayne C Hall, 2014b) and studies that only

reported lifetime cannabis use (Alterman, Erdlen, LaPorte, & Erdlen, 1982; Dervaux et al., 2002; Kazadi, Moosa, & Jeenah, 2008b; Mueser et al., 1990). The primary outcome was defined as 'relapse of psychosis', which was indexed as either (1) readmission to hospital, (2) investigator-determined relapse [operationalized in manuscript as 'psychotic episode' or exacerbation of psychotic symptoms (Koenders et al., 2014; Linszen et al., 1994; van der Meer & Velthorst, 2015)] or (3) investigator-determined relapse but without any reported criteria for operationalization (Faridi et al., 2012) (cf. *Table 10.* below). If the identified studies reported symptom scores (positive, negative), length of hospitalisation (time spent in hospital) or level of functioning [as measured with the Global Assessment of Functioning Scale (American Psychiatric, 1987)] alongside the relapse information, this data was also extracted and used in separate outcome analyses. An initial data extraction protocol was drafted in 2013 and data extraction was piloted from studies identified through a systematic search by at least two independent researchers to finalize the selection criteria and variables of interest. Data was extracted by two independent researchers. Disagreements were resolved through discussion between the researchers extracting data and a senior researcher.

Table 10. Study summary: Effects of cannabis continuation after onset and discontinuation after onset on relapse outcome

Continued Cannabis use								
Study / Country	**Definition continued cannabis use**	**Definition cannabis non-user**	**Relapse outcome**	**Length of Illness (LI) in years at FU; Illness stage (Early vs Chronic)**	**FU duration (years) [Matched YES/No]**	**N**	**d [95% CI]**	**OR [95% CI]**
Baeza et al. (2009) / Spain	Use in 1 month prior FU assessment (n=15)	No cannabis history (n=69)	Number of re-hospitalisations in 6 months FU	LI: 1 Early stage	0.5 (CAN +) 0.5 (CAN -) [YES]	84	0 [-0.57; 0.57]	N/A
Barrowclough et al. (2013) / UK	Use (any) in previous 90 days (n=160)	No use in previous 90 days (n=167)	Hospitalisation (y/n) in previous year	LI: 12 Chronic	1 (CAN +) 1 (CAN -) [YES]	327	0.33 [0.11; 0.55]	1.82 [1.22; 2.71]
Bersani, Orlandi, Kotzalidis, and Pancheri (2002) / Italy	Current user (NS) (n=54)	No cannabis history (n=71)	Number of previous hospitalisations	LI: 10 Chronic	8 (CAN +) 13 (CAN -) [NO]	125	-0.07 [-0.43; 0.29]	N/A
Caspari (1999) / Germany	Cannabis abuser (n=27) [c]	Non-abuser (n=26)	Number of rehospitalisations following index hospitalisation	LI: 7 Chronic	5 (CAN +) 6 (CAN -) [YES]	53	1.04 [0.56; 1.52]	N/A
Faridi et al. (2012) / Spain	Presence of CUD at FU (n=28)	Absence of CUD at FU (n=20)	Relapse (y/n) in 1 year FU (NS)	LI: 1 Early stage	1 (CAN +) 1 (CAN -) [YES]	48	0.04 [-0.55; 0.63]	1.08 [0.37; 3.13]
González-Pinto et al. (2009) / Spain	Continued use throughout 7 years FU (n=25)	No cannabis history (n=40)	Number of hospitalisations in 8 years FU	LI: 8 Chronic	8 (CAN +) 8 (CAN -) [YES]	65	0.58 [0.06; 1.10]	N/A
Maria Isaac, Isaac, and Holloway (2005b) / UK	+ve UDS (n=69) at admission	-ve UDS (n=46) at admission	Number of previous hospitalisations	N/A	NOT REPORTED	115	0.62 [0.24; 1.01]	N/A
Jockers-Scherubl et al. (2007) / Germany	Presence of CUD (n=19)	No Use $\leq$ 5 times/ lifetime (n=20)	Number of previous hospitalisations	LI:7 Chronic	6 (CAN +) 9 (CAN -) [NO]	39	-0.40 [-1.05; 0.26]	N/A
Koenders et al. (2014) / Netherlands	Presence of CUD (n=80)	Use $\leq$ 5 times/ lifetime (n=33)	Number of previous psychotic episodes (NS)	LI: 1 Early stage	1 (CAN +) 1 (CAN -) [YES]	113	0.12 [-0.43; 0.39]	N/A
Linszen et al. (1994) /	Presence of CUD (n=24)	Absence of CUD (n=69) in	Relapse (y/n)	LI: 3	1 (CAN +)	93	0.45	2.27

US	in 1 year FU	1 year FU	(exacerbation of psychotic symptoms[b]) in 1 year FU	Early stage	1 (CAN -) [YES]		[0.07; 0.88]	[1.05; 4.89]
Maremmani et al. (2004) / Italy	Lifetime CUD and +ve UDS (n=43)	No cannabis history (n=45)	Number of previous hospitalisations	LI: 10 Chronic	7 (CAN +) 12 (CAN -) [NO]	88	-0.08 [-0.51; 0.34}	N/A
Martinez-Arevalo, Calcedo-Ordo, and Varo-Prieto (1994) / Spain	Use during 1 year FU (NS) (n=14)	No cannabis history (n=24)	Hospitalisation (y/n) in 1 year FU	LI: 2 Early stage	1 (CAN +) 1 (CAN -)	38	0.46 [-0.23; 1.14]	2.29 [0.66; 7.91]
Negrete, Knapp, Douglas, and Smith (1986) / Canada	Use in 6 months prior to FU assessment and/or +ve UDS (n=25)	No cannabis history (n=61)	Number of previous hospitalisations	LI: 10 Chronic	6 (CAN +) 13 (CAN -) [NO]	86	0.8 [0.31; 1.29]	N/A
Peralta and Cuesta (1992) / Spain	Use > 1 time/week in year prior to assessment (n=23)	Use $\leq$ 1 time/week in year prior assessment (n=72)	Number of previous hospitalisations	LI: 5 Early stage	5 (CAN +) 6 (CAN -) [YES]	95	-0.14 [-0.62; 0.34]	N/A
Rehman and Farooq (2007) / Pakistan	Use in 1 year prior assessment (n=50)	No use in year prior assessment (n=50)	Number of previous hospitalisations	LI: 5 Early stage	4 (CAN +) 5 (CAN -) [YES]	100	0.40 [-0.002; 0.80]	N/A
Rentzsch, Buntebart, Stadelmeier, Gallinat, and Jockers-Scherübl (2011) / Germany	Current user ($\geq$ 5 days/week for $\geq$ 1 year) (n=27)	Use $\leq$ 5 times/ lifetime (n=26)	Number of previous hospitalisations	LI: 6 Chronic	5 (CAN +) 7 (CAN -) [NO]	53	0.25 [-0.31, 0.80]	N/A
Ringen et al. (2010) / Norway	Use in 6 months prior FU assessment (NS) (n=41)	No use in 6 months prior FU assessment (n=232)	Number of previous hospitalisations	LI: 8 Chronic	7 (CAN +) 9 (CAN -) [NO]	273	0.20 [-0.13; 0.54]	N/A
Salyers and Mueser (2001) / US	$\geq$ 1 time during 6 months prior FU assessment (n= 363)	Never used in 6 months prior FU (n=41)	Number of hospitalisations in 2 years prior FU assessment	LI: 8 Chronic	2 (CAN +) 2 (CAN -) [YES]	404	0.37 [0.04; 0.69]	N/A
San et al. (2013b) / Spain	Use in 4 years prior FU assessment (n=553)	No use in 4 years prior FU assessment (n=1093)	Hospitalisation (y/n) in 1 year FU	LI: $\geq$10 years for 57% of the sample Chronic	1 (CAN +) 1 (CAN -) [YES]	1646	0.25 [0.13, 0.36]	1.56 [1.27; 1.92]
G. E. Sara, P. M. Burgess, G. S. Malhi, H. A. Whiteford, and W. C. Hall (2014) / Australia	Presence of CUD in 5 years FU (n=3946)	Absence of CUD in 5 years FU (n=7672)	Number of rehospitalisations in 5 years FU	LI: > 7 Chronic	5 (CAN +) 5 (CAN -) [YES]	11618	0.92 [0.89; 0.96]	

Sorbara et al. (2003) / France	Presence of CUD in 2 years following onset (n=9)	Absence of CUD in 2 years following onset (n=49)	Hospitalisation (y/n) in 2 years following onset	LI: 2 Early stage	2 (CAN +) 2 (CAN -) [YES]	58	0.62 [0.01; 1.24]]	3.1 [1.01; 9.4]
D. van Dijk, M. W. Koeter, R. Hijman, R. S. Kahn, and W. van Den Brink (2012b) / Netherlands	$\geq$ 4 times during 1 year FU or use 1 month prior FU assessment (n=68)	< 4 times during 1 year FU or no use 1 month prior FU assessment (n=77)	Number of hospitalisations in 1 year FU	LI: 14 Chronic	1 (CAN +) 1 (CAN -) [YES]	145	0.38 [0.05; 0.71	N/A
van der Meer and Velthorst (2015) / Netherlands	Use $\leq$ 5 times/ in 3 year FU (n=146)	No cannabis history (n=257)	Number of relapses (hospitalisation and/or exacerbation of psychotic symptoms[a]) in 3 year FU	LI: 4 Early stage	3 (CAN +) 3 (CAN -) [YES]	403	0.23 [0.03; 0.43]	N/A
D Wade et al. (2006) / Australia	Presence of CUD during FU (n=40)	Absence of CUD during FU (n=48)	Relapse (y/n) (exacerbation of psychotic symptoms[b])	LI: 1.3 Early stage	1.3 (CAN +) 1.3 (CAN -) [YES]	88	0.87 [0.41; 1.33]	4.87 [2.09; 11.32]

Discontinued Cannabis use

Study / Country	**Definition discontinued cannabis use**	**Definition cannabis non-user**	**Relapse definition**	**Length of Illness (LI) in years at FU; Illness stage (Early vs Chronic)**	**FU duration (years) [Matched YES/No]**	**N**	**d (p)**	
Baeza et al. (2009) / Spain	Use at baseline but no use 1 month prior FU assessment (n=16)	No cannabis history (n=69)	Number of Rehospitalisations in 6 months FU	LI: 1 Early stage	0.5 (CAN +) 0.5 (CAN -) [YES]	85	0 [-0.57; 0.57]	N/A
González-Pinto et al. (2009) / Spain	Stopped use between onset and 7 years FU (n=27)	No cannabis history (n=40)	Number of hospitalisations in 8 years FU	LI: 8 Chronic	8 (CAN +) 8 (CAN -) [YES]	67	0.25 [-0.25; 0.75]	N/A
Maremmani et al. (2004) / Italy	Lifetime CUD but -ve UDS / (n=23)	No cannabis history (n=45)	Number of previous hospitalisations	LI: 9 Chronic	9 (CAN +) 12 (CAN -) [NO]	68	-0.08 [-0.60; 0.43]	N/A
Martinez-Arevalo et al. (1994) / Spain	No use during 1 year FU but previous use (n=25)	No cannabis history (n=24)	Hospitalisation (y/n) in 1 year FU	LI: 2 Early stage	1 (CAN +) 1 (CAN -)	49	0.02 [-0.56;	1.03 [0.36;

					[YES]		0.60]	2.95]
Negrete et al. (1986) / Canada	History of use but no use in 6 months prior FU assessment (n=51)	No cannabis history (n=61)	Number of previous hospitalisations	LI: 11 Chronic	9 (CAN +) 13 (CAN -) [NO]	112	0.22 [-0.16; 0.60]	N/A
van der Meer and Velthorst (2015) / Netherlands	Past use ≤ 5 times/ lifetime but no use in 3 year FU (n=266)	No cannabis history (n=257)	Number of relapses (hospitalisation and/or drop score on symptom scale) in 3 year FU	LI: 5 Early stage	3 (CAN +) 3 (CAN -) [YES]	523	-0.04 [-0.21; 0.13]	N/A

CI = Confidence interval; CUD = Cannabis use disorder (DSM or ICD based diagnosis of cannabis abuse or dependence); d = Effect size Cohen's d with p-value for Random Effects Model; FU = Follow up; LI = Length of illness in years at time of follow up assessment; Matched = YES if difference in follow up between CAN(+) and CAN(-) not more than 1 year, NO = if difference more than 1 year; NS = Not specified; N/A = Not applicable; OR = Odds Ratio; UDS = Urine drug screen; Stage of illness = Early stage (illness less ≤ 5 years), Chronic (illness ≥ 6 years).

[a] Based on rating scale: Comprehensive Assessment of Symptoms and History (Andreasen, Flaum, & Arndt, 1992)

[b] Based on rating scale: Brief Psychiatric Rating Scale (Overall & Gorham, 1962)

[c] Diagnosed if consumed regularly for several months and if this interfered with social functioning or was prominent during therapy. Patients with occasional use were not included

3.3.2 Quality assessment

I used a modified seven-point 'strength of reporting scale' which has been employed in previous meta-analyses conducted in a related area of research (Large et al., 2014; Mullin et al., 2012b). This scale is based on items describing methodological aspects in the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) (Von Elm et al., 2008) checklist. Studies with a score of >5 were classified as higher quality studies (cf. *aTable 5.*, Appendix III).

3.3.3 Statistical analysis

Analyses were conducted with R and its package metaphor (Viechtbauer, 2010), using random effects models (REM) (Lane, Cherek, Lieving, & Tcheremissine) that assume that effect sizes vary from study to study (Borenstein, Hedges, Higgins, & Rothstein, 2011). Effect sizes were estimated using Cohen's *d,* where *d*-values of 0.2 represent small effects, *d*-values between 0.4 and 0.6 represent moderate effect and *d*-values of 0.8 or higher indicate large effects (Cohen, 1988). *d* per study was calculated for the comparisons (1) continued cannabis use vs. non-user (CC-NC), (2) continued use vs. discontinued use (CC-DC) and (3) discontinued use vs. non-user (DC-NC). The R-package Compute.es (Del Re, 2012) was used, which allows data from included studies to be entered in the form of means and standard deviations (Ringen et al.), *p*-values for mean comparisons or chi square statistics to reach an approximated *d*. In addition, the package allowed the estimation of *d* for those studies that reported odds ratios (San et al., 2013b; Sorbara et al., 2003). In those cases where the SD was not reported (M. Isaac & Holloway, 2005; Negrete et al., 1986), the SD was extrapolated from other studies with similar outcome and sample characteristics. I carried out meta-regression analysis for categorical variables to compare the estimated *d*'s between the groups CC-NC and

DC-NC for outcome (relapse, length of hospitalisation, positive symptoms, negative symptoms, functioning). In addition, meta-regression was used to test whether the effect of cannabis was confounded by the stage of illness of participants in the studies included [i.e. early psychosis vs. chronic psychosis, with chronic psychosis referring to those subjects with an illness length of more than 5 years as classified in previous studies (Fulham et al., 2014)]. Finally, meta-regression for continuous moderators was used to test the effect of gender (percentage of sample being male) and age at the time of study assessment. The possibility of publication bias was examined using funnel plots, followed by the Egger's linear regression test (Egger, Smith, Schneider, & Minder, 1997) to test funnel plot asymmetry for significance. Homogeneity of the distribution of weighted effect sizes was tested with the *Q* test, and degree of heterogeneity was quantified using the I^2 test, which describes the percentage of observed heterogeneity that would not be expected by chance (J. P. T. Higgins, Thompson, Deeks, & Altman, 2003). I^2 values between 0 and 25% suggest small heterogeneity, while I^2 values in the range 25% and 50% suggest moderate heterogeneity, and those >50% indicate large heterogeneity.

3.3.4 Sensitivity analysis

Given the heterogeneity in the definition of relapse employed by the studies, I carried out sensitivity analyses restricting the studies to only those investigating hospital admissions, which has been reported to be a valid measure of relapse in psychosis (D. E. Addington, Patten, et al., 2013). Similarly, in the light of variation in follow-up duration between cannabis users and non-users in the studies (cf. *Table 10.* above), I carried out subset analyses by including only those studies in which cannabis users were matched to the non-users with respect to their follow up duration (indicated as

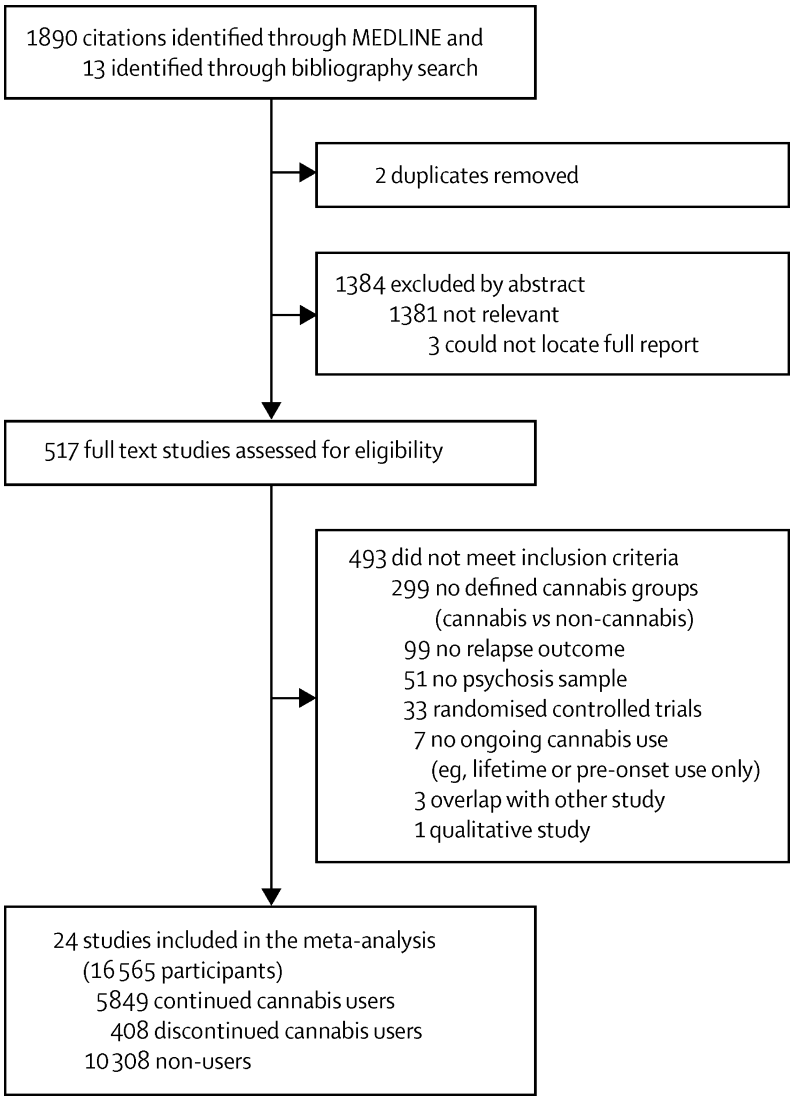
"Matched = YES" if the difference was not more than 1 year between the groups, cf. *Table 10*. above).

3.4 RESULTS

3.4.1 STUDY SELECTION

Out of 1903 identified studies, 24 met inclusion criteria, comprising 5849 individuals with continued cannabis use following psychosis onset and 10308 who were classified as non-users (cf. Flow Chart, *Figure 10.*). A subset (n=6) of the included studies included an additional group of patients that were classified as discontinued cannabis users (408 discontinued users, 268 continued users and 496 non-users).

Figure 10. Flow chart: Study selection

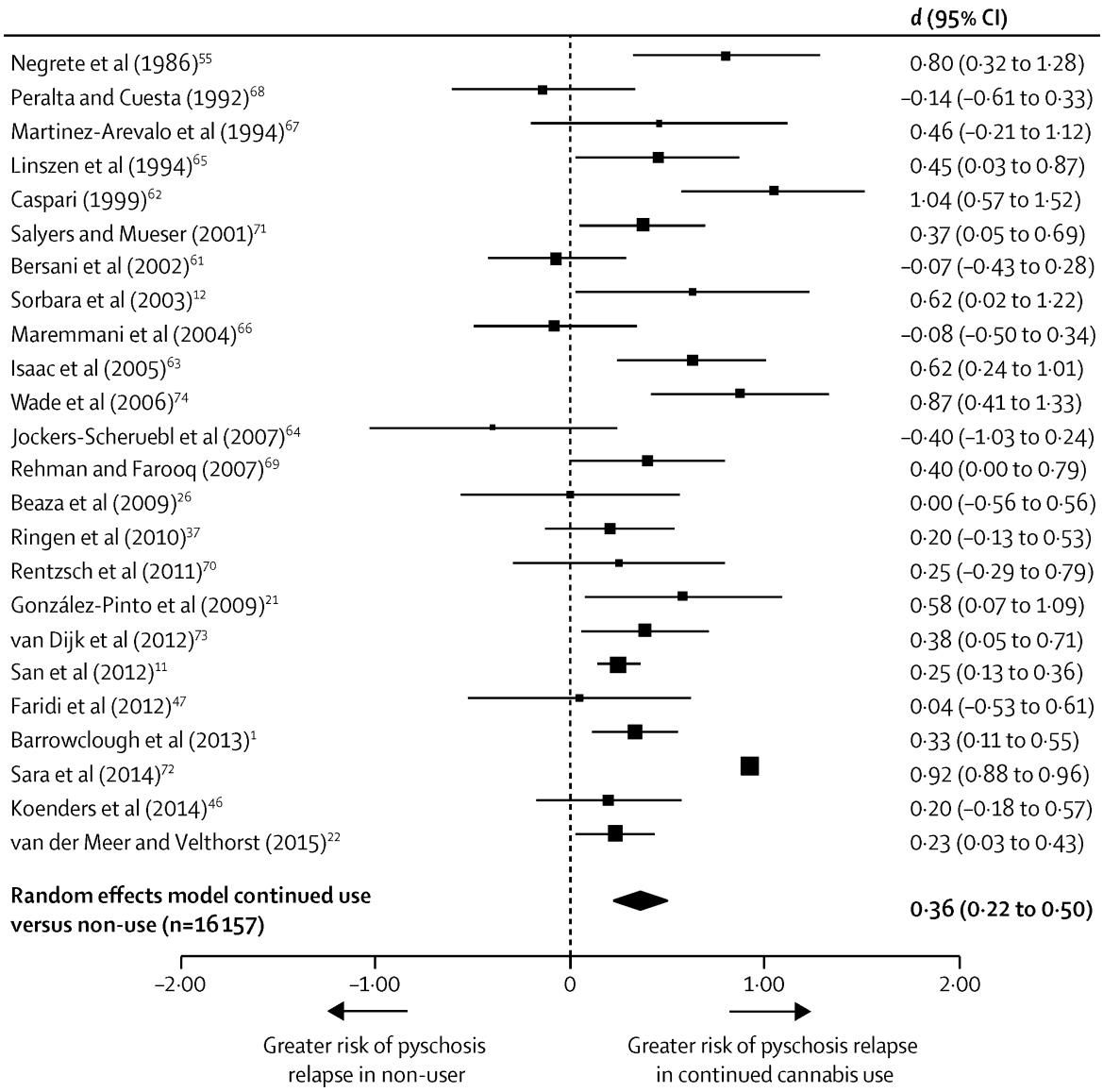


Note. Taken from Schoeler, Monk, et al. (2016)

3.4.2 Random Effects Model: Effect of ongoing cannabis use on relapse

As shown in *Figure 11.* (below), continued cannabis use post-onset of illness was significantly associated with relapse of psychosis ($d_{CC\text{-}NC}$=0.36, p<0.0001 [95% CI 0.22; 0.50]). An effect of a similar magnitude was found on length of hospitalisation after onset ($d_{CC\text{-}NC}$=0.36, p=0.02[95% CI 0.13; 0.58]).

Figure 11. Random effects model of relapse and continued cannabis use vs. non-use



Note. Taken from Schoeler, Monk, et al. (2016)

For a subset of studies (k=4, n=688) I was able to calculate the number of days spent in hospital per year of illness following onset, estimated as the weighted mean difference (WMD). The analysis was carried out using the software provided by Cochrane Collaboration, Review Manager (Rev Man 5.3) (Cochrane, 2014). One study (M. Isaac & Holloway, 2005) included in the Random Effects Model for length of hospital stay could not be included in this estimation since no precise time interval for "Number of days spent in hospital" was provided (e.g. by referring to the duration of illness for cannabis users and non-users). The results indicated that cannabis users spent

an additional 8.47 days in hospital per year of illness, although this difference was statistically not significant (p=0.20) which may reflect the lack of power (cf. *Table 11.* below).

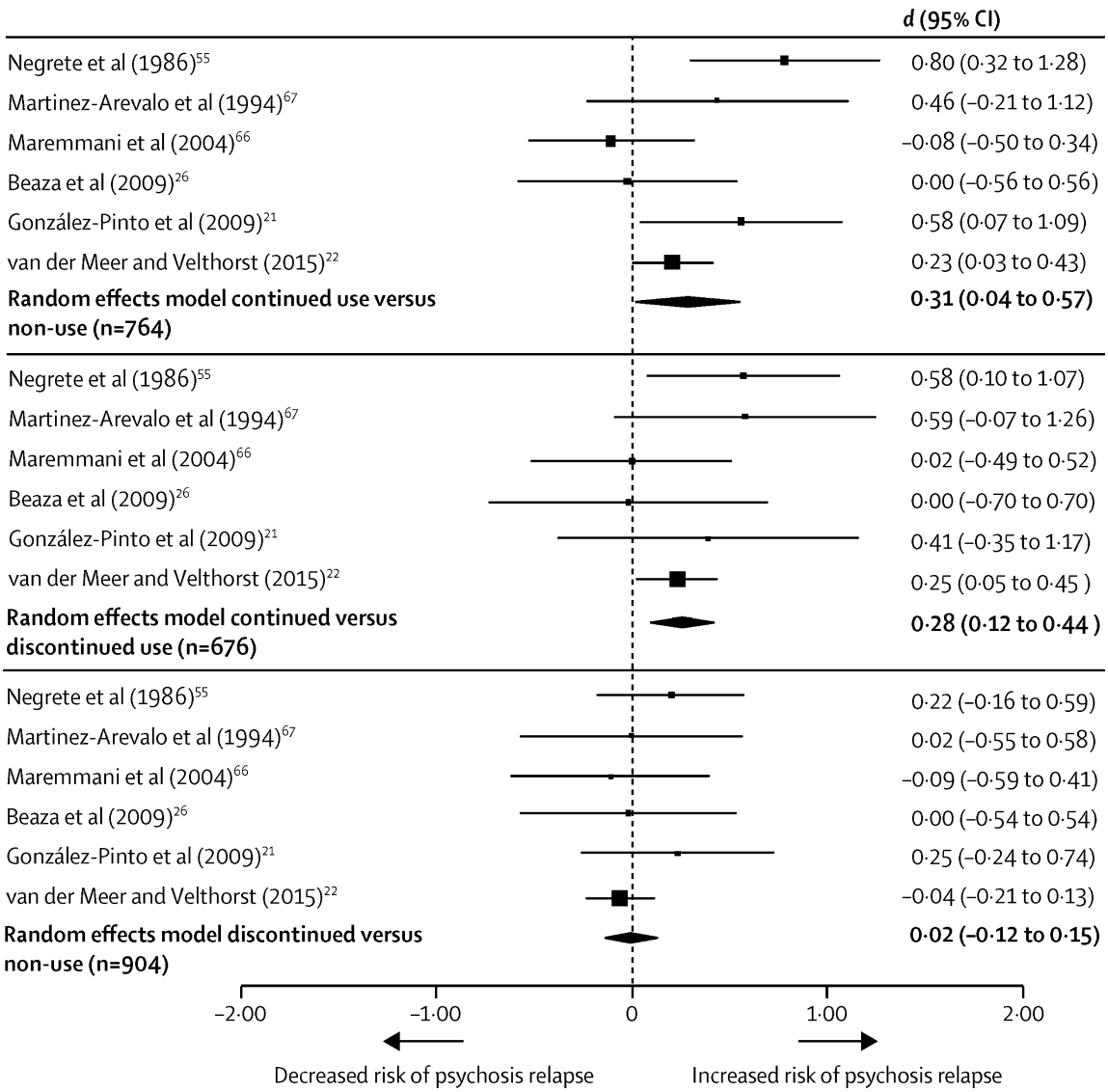
Table 11. Mean number of days spent in hospital per illness-year

	Cannabis user			**Non-user**				
Study	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Weight**	**Mean difference [95% CI]**
van Dijk et al. (2012b)	4.31	8.43	50	1.35	3.6	50	65.8 %	2.96 [0.42, 5.50]
Salyers and Mueser (2001)	36.37	29.6	19	26	33.5	20	26.4 %	10.37 [-9.45, 30.19]
Jockers-Scherubl et al. (2007)	201	156.4	68	150.4	155.7	77	6.0 %	50.60 [-0.30,101.50]
Rehman and Farooq (2007)	135	304.5	41	93	191.2	363	1.8 %	42[-53.26, 137.26]
Overall WMD	N=688 Heterogeneity: Tau² = 65.47; Chi² = 4.50, df = 3 (p = 0.21); I^2 = 33% Test for overall effect: Z = 1.27 (p = 0.20)						100. %	8.47 [-4.56, 21.50]

Note. WMD = Weighted Mean Difference

Among the studies that examined the risk of relapse (k=7, n=2298, cf. *Table 10.* above), the pooled odds were 1.97[95% CI 1.46; 2.65] times greater among those who continued to use cannabis compared with those who did not (p<0.0001). Limiting analysis to only those studies that reported on relapse rates in individuals with the three patterns of cannabis use of interest in this context, i.e. continued cannabis user, discontinued user and non-user (CC-DC-NC, k=6; N=1172) revealed that this adverse effect of cannabis in continued users remained when compared to those who discontinued ($d_{CC\text{-}DC}$=0.28, p=0.0005, [95% CI 0.12; 0.44]). In contrast, those who discontinued cannabis use did not significantly differ from the non-users in their relapse outcome ($d_{DC\text{-}NC}$=0.02, p=0.82[95% CI -0.11; 0.15]) (cf. *Figure 12*. for a summary).

Figure 12. Random effects model of relapse (continued vs. discontinued vs. non-use of cannabis)

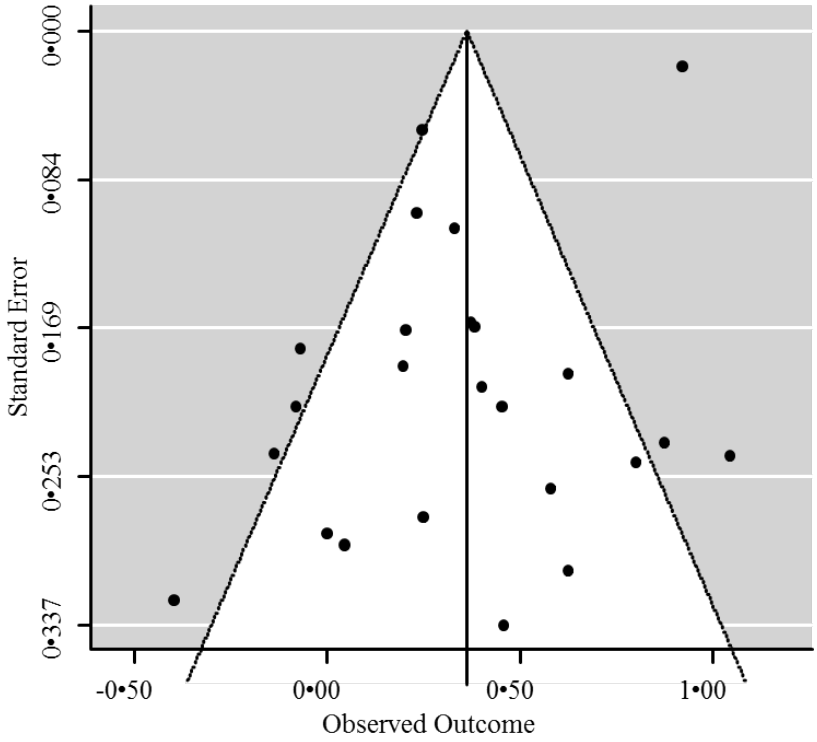


Note. Taken from Schoeler, Monk, et al. (2016)

Including all identified studies in meta-regression to compare the difference in effect size *d* between continued cannabis users and those who discontinued relative to corresponding non-user groups ($d_{CC\text{-}NC}$=0.36 vs. $d_{DC\text{-}NC}$=0.02) also confirmed that the effect-sizes were significantly different between the two sets of comparisons (p=0.04; cf. a*Table 6.*, Appendix III). Egger's test and funnels plot (cf. *Figure 13.* below and *aTable 6.*, Appendix III) indicated evidence of funnel plot asymmetry for relapse

(p=0.0002), but the trim-and-fill method (R_0 estimator) did not indicate missing studies, suggesting that the asymmetry may be due to other causes such as study heterogeneity (J. L. Peters, Sutton, Jones, Abrams, & Rushton, 2007; Terrin, Schmid, Lau, & Olkin, 2003).

Figure 13. Funnel plot for continued cannabis use and relapse



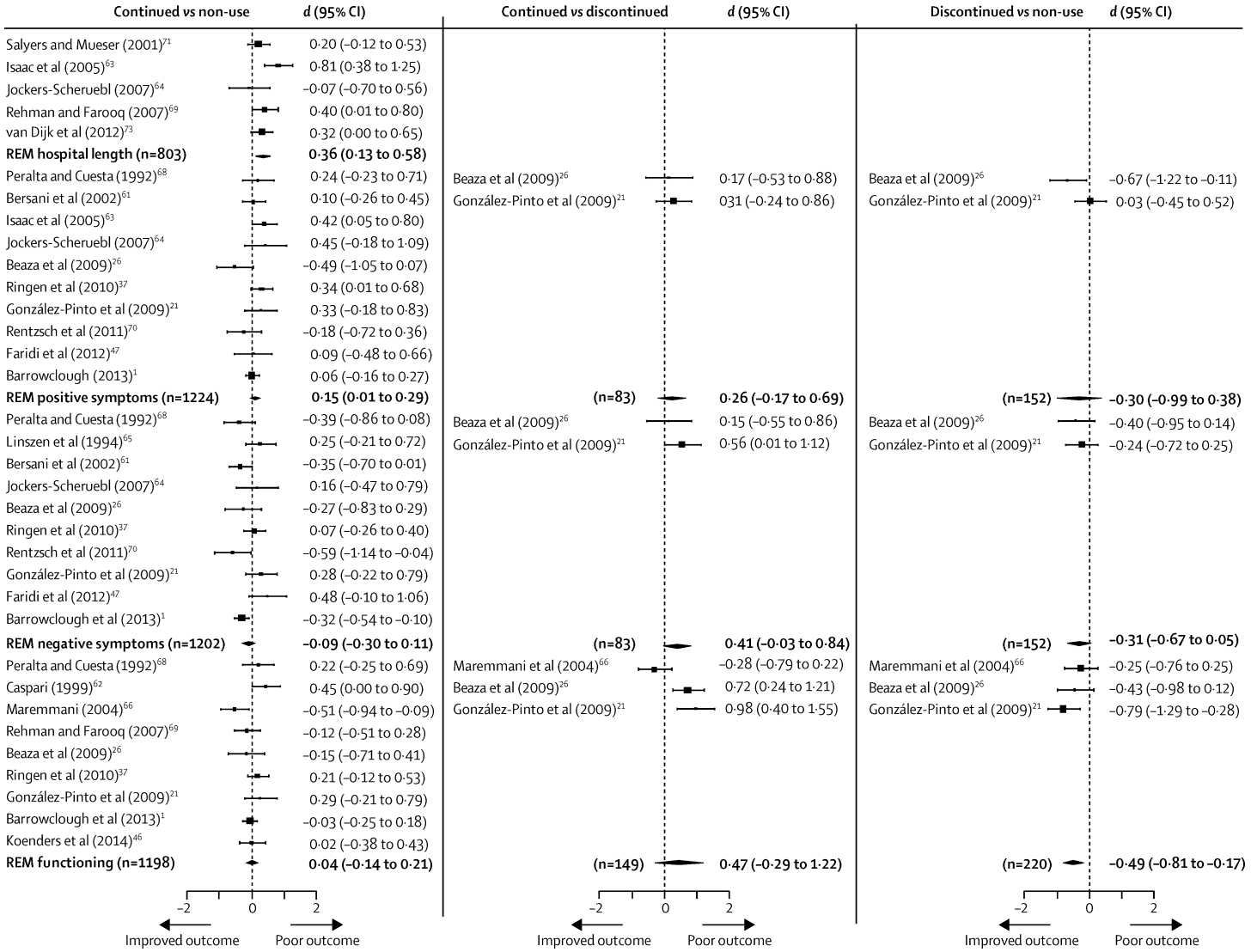
Note. Taken from Schoeler, Monk, et al. (2016)

3.4.3 Random Effects Model: Effects of ongoing cannabis use on other outcome measures

As summarized in *Figure 14.,* continued cannabis use significantly predicted positive symptom severity ($d_{CC\text{-}NC}$=0.15, p=0.04[95% CI 0.01; 0.29]). These effects on positive symptoms were not present in those who discontinued using the substance ($d_{DC\text{-}}$

$_{NC}$=-0.30, p=0.39[95% CI -0.99; 0.38]) and meta-regression indicated that the effect-sizes ($d_{CC\text{-}NC}$ vs. $d_{DC\text{-}NC}$) were significantly different (p=0.05). Interestingly, while continued cannabis users showed comparable levels of functioning when compared to the non-users ($d_{CC\text{-}NC}$=0.04, p=0.68[95% CI -0.14; 0.21]), those who discontinued using cannabis had significantly higher levels of functioning when compared to non-users ($d_{DC\text{-}NC}$=-0.49, p=0.002[95% CI -0.81; -0.17]). This difference in effect-size ($d_{CC\text{-}NC}$ vs. $d_{DC\text{-}NC}$) was significant as indicated by meta-regression (p=0.0075). Continued cannabis use was not a significant predictor for negative symptomatology ($d_{CC\text{-}NC}$=-0.09, p=0.37[95% CI -0.30; 0.11]) and there was a trend for reduced negative symptoms in those who discontinued compared to non-users ($d_{DC\text{-}NC}$=-0.31, p=0.10[95% CI -0.67; 0.05]). However, the difference in effect size ($d_{CC\text{-}NC}$ vs. $d_{DC\text{-}NC}$) was not significant (meta-regression, p=0.41). This is also in accordance with the direct comparison between continued and discontinued users (CC-DC*, cf. aTable 6.*, Appendix III), which suggested that those who continued smoking cannabis had higher levels of negative symptoms than those who discontinued. However, this was only significant at a trend level (p=0.07) and generalizability may be limited due to the few studies included in this analysis (k=2, n=83).

Figure 14. Random effects model of relapse-related outcome (continued vs. discontinued vs. non-use of cannabis)



Note. Taken from Schoeler, Monk, et al. (2016)

3.4.4 Sensitivity Analysis

There was substantial heterogeneity in the effect of continued cannabis use on relapse (83.62%, p<0.0001[95% CI 68.04%; 92.89%]). Hence, sensitivity analysis was carried out with more homogeneous groups of studies (for a summary see *Table 12.*): Studies were selected if they matched the follow up duration between continued cannabis users and non-users (cf. *Table 10.*, "Matched=YES") (k=17, n=15371, $d_{CC\text{-}NC}$=0.42, p<0.0001[95% CI 0.26; 0.57]), were rated as "high quality" (k=10, n=1366, $d_{CC\text{-}NC}$=0.50, p<0.0001[95% CI 0.32; 0.68], included either only early stage psychosis (k=10, n=1120, $d_{CC\text{-}NC}$=0.30, p=0.0004[95% CI 0.13; 0.47]) or chronic psychosis (k=13, n= 14922, $d_{CC\text{-}NC}$=0.37, p=0.0006[95% CI 0.16; 0.58]) and defined relapse as hospital admission (k=19, n=15412, $d_{CC\text{-}NC}$=0.36, p<0.0001[95% CI 0.19; 0.52]). Effect-sizes estimated for studies including only patients with non-affective psychosis (k=9, n=1280, $d_{CC\text{-}NC}$=0.34, p=0.0036[95% CI 0.11; 0.58]) and those including only affective psychosis (k=15, n=14877, $d_{CC\text{-}NC}$=0.37, p<0.0001[95% CI 0.19; 0.55] were not significantly different (p=0.89). Gender and age at follow up assessment did not significantly (p=0.87 and p=0.38) reduce the heterogeneity in relapse outcome, as indicated by meta-regression.

Table 12. Sensitivity analysis: Continued cannabis use and relapse

	k	n	*d*	*p*	CI-L	CI-U	I^2	*p* (*Q* test)
Total sample	24	16157	0.36	<0.0001	0.22	0.50	83.62%	<0.0001
Moderator: Illness Stage (*p*-mod = 0.68)								
Early stage	10	1120	0.30	0.0004	0.13	0.47	34.76%	0.1218
Chronic	13	14922	0.37	0.0006	0.16	0.58	91.00%	<0.0001
Moderator: Diagnosis (*p*-mod = 0.89)								
Non-affective	9	1280	0.34	0.0036	0.11	0.58	71.30%	0.0045
Affective	15	14877	0.37	<0.0001	0.19	0.55	85.89%	<0.0001
Moderator: Study quality (*p*-mod = 0.08)								
High (≥ score of 5)	10	1366	0.50	<0.0001	0.32	0.68	55.73%	<0.0001
Other (< score of 5)	14	14791	0.25	0.0104	0.06	0.44	87.70%	<0.0001
Moderator: Matched follow up years (*p*-mod = 0.07)								
Yes	17	15378	0.42	<0.0001	0.26	0.57	84.20%	<0.0001
No	6	664	0.13	0.4019	-0.17	0.42	63.03%	0.0259
Moderator: Relapse definition (*p*-mod = 0.97)								
Hospital admission	19	15412	0.36	<0.0001	0.19	0.52	86.27%	<0.0001
Other/unspecified	5	745	0.35	0.0047	0.11	0.59	50.43%	<0.0001
Male gender (% per study)	k=20; *p*-mod=0.87; coefficient estimate= -0.0008							
Age at date of follow up assessment	k=22; *p*-mod=0.38; coefficient estimate= 0.0116							

Note. *d*= Cohen's *d*; k=number of studies, n=number of subjects; *p* (Murat Yücel et al.) = *p*-value for moderator in meta-regression; *p* (*Q* test) = *p*-value for *Q* test for heterogeneity.

3.5 DISCUSSION

To my knowledge, this is the first meta-analysis to demonstrate that, regardless of the stage of their psychotic disorder, patients who continue using cannabis are more likely to suffer from a relapsing course when compared both to non-using patients (d_{CC-NC}=0.36) and to patients who discontinue using the substance after onset (d_{CC-DC}=0.28). Furthermore, considering that those who discontinue do not differ from the non-users in their relapse outcome (d_{DC-NC}=0.02), these results suggest that the increased relapse rate associated with cannabis use may resolve following discontinuation of its use. Gradient in the effect of cannabis use (continued use > discontinued use > non-use) on outcome in psychosis observed in the present analysis is consistent with that noted in other studies not included here (Grech et al., 2005b; B. G. Schimmelmann et al., 2012), with the effect on outcome being most adverse in those who continue to use the drug. This is also compatible with other epidemiological evidence of the adverse effects of cannabis being dose-dependent (Hides et al., 2006; Linszen et al., 1994) and with evidence that the magnitude of cognitive impairments associated with cannabis exposure tend to diminish following abstinence (Rabin, Zakzanis, Daskalakis, & George, 2013). Additionally, my results suggest that continued cannabis users suffered significantly longer hospitalisations following their onset than non-users (d_{CC-NC}=0.36), which may suggest perhaps more severe relapses requiring longer inpatient care to stabilize. It is worth noting that longer hospital stay may also be related to other factors unrelated to the severity of the illness, such as lack of suitable accommodation for the patient to be discharged to.

In terms of symptomatic outcome, continued cannabis users experienced more severe positive psychotic symptoms at follow-up assessment. This effect was not present in those who discontinued using the substance (d_{CC-NC}=0.15 vs. d_{CC-DC}=-0.30).

This is consistent with other follow-up studies that compared positive symptom levels between continued users, discontinued users and non-users of cannabis (Clausen et al., 2013; B. G. Schimmelmann et al., 2012; J. M. Stone et al., 2014; van der Meer & Velthorst, 2015) and a report from a longitudinal population-based sample suggesting that continuation of cannabis use predicted subsequent persistence of psychotic symptoms (Kuepper et al., 2011a). Other studies have reported a temporal association between changes in cannabis use and subsequent changes in psychotic symptom severity, both in the short (Degenhardt et al., 2007) and long-term (Foti et al., 2010). Evidence that cannabis use has a particularly harmful effect on different outcome measures of psychosis (relapse, psychotic symptoms) when use is continued compared to when one stops using is intuitive and consistent with effects of cannabis use on cognition (Rabin et al., 2013). However, the effect of cannabis and continuity of its use was not observed across certain other domains of outcome in the present meta-analysis: continued cannabis users did not differ from the non-user groups in their negative symptomatology ($d_{CC\text{-}NC}$=-0.09, p=0.37). A similar result was reported in a separate meta-analysis focusing on symptoms (Large et al., 2014). Discontinued users also did not differ significantly from non-users ($d_{DC\text{-}NC}$=-0.31, p=0.10), though they had less negative symptoms when compared directly with continued users ($d_{CC\text{-}DC}$=0.41, p=0.07). This may appear to contradict the results of the meta-regression suggesting no difference between the effects of continued and discontinued use on negative symptoms. However, it is worth noting that meta-regression compared the estimates from two different random effects models (i.e., $d_{CC\text{-}NC}$ and $d_{DC\text{-}NC}$) examining effect on negative symptoms, rather than a direct comparison between discontinued and continued cannabis users. Furthermore, while the direct comparison involved data from only two studies, the meta-regression compared data from a larger sample of studies.

Nevertheless, it is worth noting that the general direction of effect in different groups is consistent across all comparisons. Continued cannabis users showed similar levels of functioning when compared to the non-users ($d_{CC\text{-}NC}$=0.04, p=0.68), while discontinued users had better functioning scores compared to non-users ($d_{DC\text{-}NC}$=-0.49, p=0.002). In line with this, other studies have reported that those who discontinue cannabis have better functioning (Baeza et al., 2009; Clausen et al., 2013; B. G. Schimmelmann et al., 2012; van der Meer & Velthorst, 2015) compared to non-users and a recent meta-analysis suggested that cessation of substance use in general was associated with improvement of negative symptoms and global functioning (Mullin et al., 2012b). These findings suggest that cannabis-using patients may have better functioning to begin with (though this is not something that could be tested in the present analysis). This is also compatible with the view that cannabis-using patients represent a subgroup with a less neurodevelopmental pathology (Ferraro et al., 2013; Murat Yücel et al., 2012); perhaps for this reason the adverse effects of cannabis use on functioning and negative symptoms only become apparent when continued users are compared to those who discontinued use rather than non-users. Patients who are able to stop using cannabis may also represent an etiologically and clinically distinct subgroup suffering from a less severe illness with less of a need to use cannabis for self-medication. The observed association between cannabis exposure and relapse of psychosis and related outcome variables may be mediated through the effect of its key psychoactive ingredient, THC, on the neural substrates implicated in psychosis (Sagnik Bhattacharyya, Atakan, et al., 2015a; S. Bhattacharyya, Z. Atakan, et al., 2012; S. Bhattacharyya, Crippa, Allen, & et al., 2012; Sagnik Bhattacharyya et al., 2014; S. Bhattacharyya et al., 2009; Cortes-Briones et al., 2015). The observed strength of association between continued cannabis use and relapse is comparable to other

identified environmental risk factors for relapse of psychosis such as high expressed emotions (*d*=0.31) (Butzlaff & Hooley, 1998a), as well as the effects of interventions that prevent relapse, such as psychoeducation (*d*=0.21) (Lincoln, Wilhelm, & Nestoriuc, 2007) or reduce psychotic symptoms, such as antipsychotic treatment (*d*=0.48) (S Leucht, Arbter, Engel, Kissling, & Davis, 2009). Hence, these results emphasize the importance of cannabis use as a clinically relevant target for treatment development.

3.5.1 LIMITATIONS

Some limitations are noteworthy, which are mainly related to the methodological heterogeneity among the studies included (cf. *Table 10.* above). Different criteria were applied by the studies included in this meta-analysis to classify those who continued to use cannabis (e.g. presence of cannabis use disorder/use more than once in a defined time-period), or discontinued the drug (e.g. history of use but negative UDS/no use in given time period), as well as non-users (e.g. less than daily use/non-abuser/no use in given time period/never use). Follow-up durations also differed between cannabis users and non-users in some studies [e.g. 7 year relapse window for cannabis users vs. 12 year relapse window for non-users in Maremmani et al. (2004)]. In fact, excluding those studies with differing follow-up windows between the participant groups as part of sensitivity analysis revealed a slightly larger effect of cannabis use on relapse than found in the main analysis (*d*=0.42 vs. *d*=0.36). The study by Baeza et al. (2009) may need to be highlighted in this context, considering that their report of absence of adverse effects of cannabis use on relapse may reflect their six months follow up, an interval perhaps too short to detect differences in relapse rates between the groups.

It may be argued that the patients differed in their stage of illness across the included studies (e.g. early stage vs. chronic psychosis), but sensitivity analysis revealed that this did not significantly influence the results. It was not possible to control for the effect of other potential confounding factors that may be associated with cannabis use such as medication adherence (Barrowclough et al., 2013; Clausen et al., 2013; Martinez-Arevalo et al., 1994; Rehman & Farooq, 2007; B. G. Schimmelmann et al., 2012), engagement with the services (B. G. Schimmelmann et al., 2012) or other abuse of other drugs (Barrowclough et al., 2013). However, the present results are also consistent with studies that have systematically controlled for age, gender, alcohol and drug use, illness characteristics (e.g. duration, diagnosis, severity) and medication adherence when measuring the effect of cannabis use on relapse (San et al., 2013b; Sorbara et al., 2003; van Dijk et al., 2012c). Another limitation inherent to the meta-analytical design relates to our inability to analyse raw data, which limited my ability to carry out moderation analysis to directly test for more defined dose-response patterns such as frequency, duration or age of onset of use or type of cannabis consumed - factors that are also likely to moderate the effect of cannabis on relapse (Hides et al., 2006; Linszen et al., 1994). A further potential source of heterogeneity may be related to the use of different types of cannabis containing differing proportion of the main ingredients such as delta-9-tetrahydrocannabinol or Cannabidiol that are known to have opposing effects (Sagnik Bhattacharyya et al., 2010b). However, I was unable to assess the effect of type of cannabis used, as this information was not available for the included studies. Finally, although our systematic search may have been somewhat restricted by using MEDLINE only, I aimed to address this potential limitation by screening bibliographies from previous conducted meta-analyses, systematic reviews

and original studies for additional studies that may have been missed out in the database search.

Nevertheless, despite lack of more fine-grained measures, this meta-analysis detected a fairly robust pooled effect of continued cannabis exposure on relapse outcome and other measures suggestive of adverse outcome, which were absent in those who discontinued use of the drug. The fact that the effects of continued use of cannabis or its discontinuation are consistent across different measures of outcome only serves to underline the importance of addressing continued cannabis use in patients with psychosis in the clinical setting, by highlighting that outcomes are likely to be better in those who discontinue the drug.

3.6 **PAPER 4:** CORRELATION STILL DOES NOT IMPLY CAUSATION

Following the publication of the meta-analysis, *Lancet Psychiatry* has received a correspondence letter, in which the issue of causality was raised. The correspondence letter (Ksir & Hart, 2016b) as well as my response to the letter (Schoeler, Murray, et al., 2016) are printed below:

3.6.1 CORRESPONDENCE LETTER

From Ksir and Hart (2016b): *"We read with intense interest the meta-analysis by Schoeler and colleagues (Schoeler, Monk, et al., 2016) on continued cannabis use in patients with psychosis. Clearly, this issue is timely and important, and the authors should be commended for attempting to provide empirical evidence to inform public policy. However, our enthusiasm was dampened because the interpretation extends beyond the available data.*

It is of utmost importance for us to remember that the meta-analysis was based on correlational studies. Each study points out that causation has not been shown; however, a strong tendency exists to accept cannabis use as a so-called component cause of psychosis, which then leads to the conclusion that it is imperative to reduce cannabis use in patients with or at risk for psychosis. Although we understand this impulse is motivated by a concern for public health, we should not allow the consistency of these correlational findings to substitute for actual evidence of causality.

In 2016, we did a critical review (Ksir & Hart, 2016a) of the scientific literature on cannabis and psychosis and concluded that the literature supports the hypothesis that both psychosis and cannabis use are more likely in individuals with a shared vulnerability to misuse of various substances and increased risk for various mental disorders. In other words, the correlation between cannabis use and psychosis is not specific, either with regard to the chemicals found in cannabis or to psychosis as

opposed to other disorders.

Schoeler and colleagues (Schoeler, Monk, et al., 2016) stated that rates of cannabis use in patients with psychosis are "higher than…those of people with other psychiatric diagnoses". To support this statement the authors cited an article by Agosti and colleagues (Agosti, Nunes, & Levin, 2002a), even though Agosti and colleagues clearly concluded, "Alcohol dependence, antisocial personality disorder, and conduct disorder had the strongest associations with cannabis dependence, followed by anxiety and mood disorders". They did not report any association between cannabis and psychosis, presumably because of the low frequency of psychosis in the participants studied.

In our own review (Ksir & Hart, 2016a), we included seven studies published in the past 3 years that provided information on the issue of specificity. After reviewing the scientific literature we found evidence that bipolar disorder, anxiety disorder, and mood disorder have all been correlated with cannabis use, and reported that psychosis has been correlated with heavy tobacco smoking, heavy alcohol use, stimulant misuse, and sedative misuse. We found no clear evidence for a causal relation between cannabis and psychosis (Ksir & Hart, 2016a).

According to our shared vulnerability hypothesis, in a given group of cannabis users who have had psychotic episodes, the individuals with the greatest degree of the shared vulnerability would be the most likely to continue cannabis use rather than to discontinue, and they would be the most likely to have recurring episodes of psychosis and require more hospital treatment. As such, these two outcomes should be correlated, even if neither is a cause of the other.

As to whether a public health benefit can be obtained from efforts to reduce cannabis use in patients with psychosis, two randomised controlled trials (Hjorthøj et

al., 2013; Madigan et al., 2013) published in 2013, comparing treatment as usual with treatment as usual plus motivational interviewing and cognitive behaviour therapy that focused on cannabis use, found no beneficial effect of either intervention on either psychotic symptoms or amount of cannabis use.

Our greatest concern is not that someone might be advised to stop using cannabis. We are concerned that a misunderstanding of the relation between cannabis use and psychotic behaviour leads to an oversimplification of the complex developmental nature of substance use and mental disorders. Furthermore, we propose that future studies that limit their data collection to focus only on cannabis and only on psychosis will do little to enhance our understanding of the complexity of this comorbidity."

3.6.2 AUTHORS' REPLY

From Schoeler, Murray, et al. (2016): "*We thank Charles Ksir and Carl Hart for their interest in our Article (Schoeler, Monk, et al., 2016). We agree that we cannot draw definite conclusions regarding causality from our meta-analysis of cannabis use continuation versus discontinuation in people already psychotic. This was not our purpose because there are already both prospective and experimental studies implicating cannabis use as "a component cause" for psychotic symptomatology (Robin M. Murray & Di Forti, 2016). In this regard we should point out that contrary to the authors' assertion, Agosti and colleagues (Agosti et al., 2002a) did in fact find an increased risk (odds ratio 3.49, 95% CI 1.35–9.02) of psychosis in patients dependent on cannabis.*

Ksir and Hart suggest that the association between continued cannabis use and psychotic relapse is the result of a "shared-vulnerability", presumably genetic. However, two recent GWAS studies suggest that the overlap in genetic vulnerability for

psychosis and cannabis use is likely to be only modest (cf. aSupplementary 1, Appendix III). Furthermore, the association of cannabis use with psychotic symptomatology remained significant when the main effect of genetic predisposition was fully (David M Fergusson et al., 2005; Foti et al., 2010) or partly factored out (cf. aSupplementary 1, Appendix III). Dose–response relationships in those studies further oppose a shared-vulnerability hypothesis. Contrary to Ksir and Hart's assertion, shared vulnerability also does not explain why discontinuation of cannabis use might be associated with a reduced severity of symptoms in the same individuals who had more severe symptoms while they were using cannabis (Foti et al., 2010). Finally, the notion of cannabis use as a risk factor does not contradict the results from the two randomised controlled trials cited by the authors. Considering that the interventions were not effective in reducing cannabis use in those studies (cf. aSupplementary 1, Appendix III), no differences in outcome between the two intervention groups would be expected, which was the case. Although we appreciate Ksir and Hart's advice for caution, on the basis of the available evidence, we would argue that it seems unlikely that shared genetic vulnerability fully accounts for the association between continued cannabis use and relapse in psychosis."

4 PAPER 2: EFFECTS OF CONTINUATION, FREQUENCY AND TYPE OF CANNABIS USE ON RELAPSE IN THE FIRST TWO YEARS FOLLOWING ONSET OF PSYCHOSIS - AN OBSERVATIONAL STUDY

4.1 ABSTRACT

Background. Although cannabis use following a first episode of psychosis (FEP) has been associated with relapse, current understanding is limited regarding the determinants of this most preventable risk factor for relapse of psychosis.

Methods. 256 FEP patients presenting to psychiatric services in South London were prospectively recruited and followed up. Relapse of psychosis within two years following onset of psychosis was defined as risk of subsequent admission to hospital. Patients were classified into different patterns of cannabis use based on (a) continuity of use following onset of psychosis, (b) potency of cannabis consumed and (c) frequency of use following onset of their illness. Multiple regression analyses (logistic/binominal) were employed to compare the different cannabis use groups. Propensity score analysis was used to validate the results.

Findings. Simple analyses showed that former regular users who stopped after onset had the most favourable illness course with regard to relapse. In multiple analysis, continued high-frequency users (daily use in all 24 months) of high-potency cannabis ("skunk-like") had the worst outcome, indexed as an increased risk for a subsequent relapse (OR=3.28; 95%CI[1.22-9.18]), more numerous relapses (p=0.07), fewer months until a relapse occurred (p=0.02) and more intense psychiatric care (p=0.01) following onset of psychosis.

Interpretation. Adverse effects of continued use of cannabis following the onset of FEP depend on the specific patterns of use. Interventions may focus on persuading

cannabis-using patients with psychosis to reduce use or shift to less potent forms of cannabis.

4.2 INTRODUCTION

There is good grounds to believe that cannabis use is a contributory cause of psychotic disorders, especially if used frequently and initiated at an early age (T. H. M. Moore et al., 2007; Stepniak et al., 2014). Cannabis remains the most commonly used illicit drug in patients with established psychosis (Moore, Mancuso, Slade, Galletly, & Castle, 2012) and rates are particularly high in young people presenting with their first episode of psychosis (Patel R et al., 2016). Relatively few patients with established psychosis start using cannabis after onset of psychosis (González-Pinto et al., 2011), but a major concern is the substantial proportion that continues using the drug (Faridi et al., 2012; Hinton et al., 2007). A recent meta-analysis suggests that continued cannabis use following onset predicts poor outcome in psychosis as indicated by higher number of relapses, hospitalisation and more severe positive symptomatology (Schoeler, Monk, et al., 2016), consistent with evidence that experimental administration of the key psychoactive ingredient in cannabis is associated with transient psychotic symptoms and cognitive impairments in healthy individuals and exacerbation of symptoms in patients with a pre-existing psychotic disorder (Sagnik Bhattacharyya et al., 2009; D'Souza et al., 2005). However, whether the association between cannabis use and worse outcome in pre-existing psychosis is causal in nature has remained inconclusive (Schoeler, Monk, et al., 2016) because prospective evidence to date has not always successfully established that cannabis use actually preceded and was in reasonable temporal proximity to the outcome interest, i.e. relapse of psychosis. More importantly, how parameters of cannabis use, such as type and potency of cannabis used and frequency of use affect outcome has remained unclear. This is especially important in light of evidence that dose, type and pattern (Di Forti, Marconi, et al., 2015) of cannabis use are important determinants of its effect on onset of psychosis. In particular, for such

evidence to be translated into real world meaningful solutions in the clinical setting, it is important to develop a more nuanced understanding of the association between one of the most potentially preventable risk factors of psychosis, i.e., cannabis use and its determinants and the risk of relapse in psychosis.

Understanding the role of cannabis in relapse of psychosis is important not just because prevention of relapse is critical for better long-term outcome in psychosis (Wiersma et al., 1998), but also because of the substantial financial implications associated with need for hospital care in those who relapse (Knapp, Locklear, & Järbrink, 2009b), as upto 50% of first-episode psychosis (FEP) patients experience a relapse that results in hospital admission within the first 2 years of illness, with the risk increasing to over 80% by the 8th year (M Alvarez-Jimenez et al., 2012).

In the current study I aim to address the limitations in existing evidence [cf. *Table 13*. and Schoeler, Monk, et al. (2016)], such as lack of detailed assessment of cannabis use pattern following onset of psychosis, modest sample size and lack of consideration of potentially important confounders, by investigating the effects of continued cannabis use on risk of relapse as indexed by hospital admission over the first two years following onset of psychosis. I employ a precise definition of continued use (use at least once within each month throughout the two years following the onset of illness), examine dose-response relationships that incorporate potency of cannabis consumed and address the effects of potential confounders such as medication non-adherence (Caseiro et al., 2012; Leeson et al., 2012), illness severity at onset (Baeza et al., 2009; Hinton et al., 2007), ethnicity (N. Goater et al., 1999), gender (Moore et al., 2012) and other drug use such as alcohol use, cigarette use or other illicit drug use (Opsal et al., 2011) and repeated these analyses in propensity score-matched groups.

Table 13. Follow up studies investigating the effect of cannabis profiles on relapse outcome in first episode psychosis patients

Study / Country	**Study time points (T)**	**Cannabis profiles** *NU: Non-user SU: Started user CU: Continued user*	**Comparison**	**Relapse definition**	***d* [95% CI]**	**OR[a] [95% CI]**	***p***	**Controlled confounders**	**N**	**Quality [b]**
Sorbara et al. (2003)/ France	T1: Onset (age 31) T2: 24 Months FU	NU: Absence of CUD between T1 and T2 SU/CU: Presence of CUD between T1 and T2	(NU) vs. (SU/CU)	Readmission to hospital (y/n)		3.1 [1.01-9.4]	0.05	Age, sex, diagnosis, medication adherence, DUP	58	1: (+) 2: (–) 3: (–)
				Compulsory readmission (y/n)		3.4 [1-12.2]	0.06			
Darryl Wade, Harrigan, McGorry, Burgess, and Whelan (2007)/Australia	T1: Onset (age 20) T2: 15 Months FU	NU: Absence of CUD between T1 and T2 SU/CU: Presence of CUD between T1 and T2	(NU) vs. (SU/CU)	Relapse (y/n) (exacerbation of psychotic symptoms, BPRS)		4.87 [2.09-11.32]	0.0003	-	88	1: (–) 2: (–) 3: (–)
Baeza et al. (2009) / Spain	T1: Onset (age 16) T2: 6 Months FU	NU: no use 1 month prior T1 FU: use 1 months prior T1, no use 1 month prior T1 SU/CU: use in 1 month prior FU assessment	(NU) vs. (SU/CU)	Number of re-hospitalisations	0 [-0.57-0.57]		1	-	84	1: (–) 2: (–) 3: (–)
González-Pinto et al. (2011)/ Spain	T1: Onset (age 30) T2: 8 Y FU	NU: never user SU: stopped use SU/CU: continued or started use	(NU) vs. (FU) vs. (SU/CU)	Number of hospital admissions (T1-T2)	0.58 [0.06-1.10]		0.03	-	65	1: (–) 2: (–) 3: (–)
Leeson et al. (2012)/ UK	T1: Onset (age 26) T2: 24 Months FU	FU: use 1 year prior to T1, no use 3 months prior T2 CU: use at T1, use 3 months prior T2	(NU) vs. (CU)	Number of days spent in hospital (T1-T2)	1.04 [0.39-1.68]		<0.0001	-	50	1: (–) 2: (–) 3: (–)
Caseiro et al. (2012)/ Spain	T1: Onset (age 27) T2: 36 Months FU	NU: no use at T1 and T2 CU: use at T1 and T2 (≥ 1 times/week for at least a year)	(NU) vs. (CU)	Relapse (y/n)[c]		0.91 [0.65-1.29][d]	0.65	AoO, DUP, SAPS, SANS, BPRS, PAS, insight, family	140	1: (+) 2: (–) 3: (–)

								history, academic level, medication adherence		
Faber et al. (2012)/ Netherlands	T1: Onset (age 28) T2: 6 Months FU T3: 15 Months FU T4: 24 Months FU	NU: no use T1 and T4 (<1 time) SU/CU: use between T1 and T4 (≥ 1 time)	(NU) vs. (SU/CU)	Symptomatic non-remission (T1-T4)		1.09 [0.58-2.09]	0.78	-	124	1: (–) 2: (–) 3: (–)
				Months in relapse (T1-T4)	0.03 [-0.41-0.46]		0.9			
Faridi et al. (2012)/ Canada	T1: Onset (age 22) T2: 12 Months FU	NU: Absence of CUD between T1 and T2 CU: Presence of CUD at T1 and T2	(NU) vs. (CU)	Relapse yes/no (NOS)		1.08 [0.38-3.13]	0.89	-	48	1: (–) 2: (–) 3: (–)
				Risk of continuous illness course (NOS)		1.16 [0.40-3.38]	0.78			
L. Clausen et al. (2014)/ Denmark	T1: Onset (age 27) T2: 5 Y FU	NU: no use at T1 and T2 FU: stopped between T1 and T2 SU: started between T1 and T2 CU: continued between T1 and T2	(NU) vs. (CU)	Number of days spent in hospital (T1-T2)	0.07 [-0.35-0.48]		0.76	-	228	1: (–) 2: (–) 3: (+)

Note. BPRS = Brief Psychiatric Rating Scale (Overall & Gorham, 1962); DUP = Duration of untreated psychosis; CGI = Clinical Global Impression scale (W Guy, 1976); CUD = Cannabis Use Disorder; FU= Follow up; *d*= effect size Cohen's *d*; NOS = Not otherwise specified; OR= Odds Ratio; PAS = Premorbid Adjustment Scale (Cannon-Spoor, Potkin, & Wyatt, 1982a), SANS = Scale for the Assessment of Negative (Andreasen, 1989b); SAPS = Scale for the Assessment of Positive Symptoms (Andreasen, 1984a)

[a]OR and Cohen's *d* reported as applicable to results reported in original study

[b]Quality assessment based on whether a study did (+) or did not (–): 1: Control for confounders; 2: Based cannabis profile on multiple cannabis-parameter (e.g. frequency/duration/type); 3: Included adequate sample size (>200)

[c]Relapse based on either (1) BPRS score or (2) CGI rating or (3) hospitalisation or (4) completed suicide

[d]Adjusted Hazard Ratio

4.3 METHOD

4.3.1 SAMPLE

Patients with first-episode non-organic [non-affective (ICD10 codes F20-F29) or affective (F30-F33)] psychosis (WHO, 2004), aged 18-65 who were referred to local psychiatric services in South London were recruited into the study. They were assessed twice, first close to the onset of their illness using face-to-face interviews and subsequently for follow-up, using either a face-to-face or a telephone interview (if the individual was unable to appear in person). Face-to-face or phone interview data was complemented by a screening of their clinical records to extract healthcare usage data (e.g. dates of admission/discharge, information on involuntary admission, medication usage). All patients were followed up for at least two years following the onset of their illness. I focused on this early stage following onset of psychosis as this is considered as the "critical period" that determines long-term outcome in psychosis (Birchwood et al., 1997). Follow-up assessments were carried out until September 2015. Data from clinical records regarding hospital admissions were also collected for those who refused to take part in the follow-up interview (n=133) over the same 2-year window following onset of psychosis. Risk of relapse was not significantly different (36.3% vs. 38.3% relapsed, χ^2= 0.15, p=0.70) in those patients who agreed to take part (n=256) in the follow-up (Completers) compared to those who refused (Refusers). Furthermore, the two groups (Completers and Refusers) did not significantly differ in baseline characteristics such as premorbid cannabis use (ever used prior onset), gender, ethnicity and age of onset of psychosis (cf. *Table 14.* below). When considering separately those who relapsed and those who did not over the 2-year follow-up period, Completers and Refusers did not significantly differ in these baseline characteristics (cf. *Table 14.*). This study was granted ethical approval by South London & Maudsley NHS foundation trust

and Institute of Psychiatry Local Research Ethics Committee. All subjects included in the study gave written informed consent (cf. **Chapter 8.2.1**, Appendix II).

Table 14. Group comparisons (Completers vs. Refusers) in baseline characteristics

Sample (Total)	Completers (n=256)	Refusers (n=133)	χ^2	*p*
Relapse (yes)	93 (36.3%)	51 (38.3%)	0.15	0.7
Premorbid cannabis use (yes)	193 (75.4%)	98 (73.7%)	0.14	0.71
Gender (male)	156 (60.9%)	88 (66.2%)	1.02	0.31
Ethnicity (non-white)*	170 (66.4%)	69 (65.1%)	0.06	0.81
Age of onset (<21)	48 (18.8%)	22 (16.5%)	0.29	0.59
Subsample (Not relapsed)	Included (n=163)	Refused (n=82)	χ^2	*p*
Premorbid cannabis use (yes)	117 (71.8%)	60 (73.2%)	0.05	0.82
Gender (male)	101 (62%)	58 (70.7%)	1.84	0.17
Ethnicity (non-white)	99 (60.7%)	44 (63.8%)	0.19	0.66
Age of onset (<21)	26 (16%)	12 (14.6%)	0.07	0.79
Subsample (Relapsed)	Included (n=93)	Refused (n=51)	χ^2	*p*
Premorbid cannabis use (yes)	76 (81.7%)	38 (74.5%)	1.04	0.31
Gender (male)	55 (59.1%)	30 (58.8%)	0.001	0.97
Ethnicity (non-white)	71 (76.3%)	25 (67.6%)	1.06	0.31
Age of onset (<21)	22 (23.7%)	10 (19.6%)	0.31	0.58

* missing data (refusers) for n=27

4.3.2 MEASURES

Cannabis use was assessed using a modified version of the Cannabis Experience Questionnaire (CEQ_{mv}, cf. **Chapter 8.2.2**, Appendix II) (Di Forti, Marconi, et al., 2015), collecting data on premorbid cannabis use, as well as use over the first two years following onset of psychosis. To assess the reliability of the retrospective assessment of cannabis use, I compared data for n=206 subjects on premorbid cannabis use (ever used before onset) collected at onset of psychosis with data on premorbid cannabis use reported at follow up. In 92.7% of those compared, reporting of premorbid cannabis use was consistent across both assessments (i.e., at onset and at follow-up); 3.4 % those

who denied premorbid use when assessed at the onset of psychosis admitted it when re-examined at the follow up assessment, while 3.9% denied pre-morbid cannabis use at follow-up assessment although they had admitted use when assessed at onset. Cannabis users were classified based on their pattern of use into different cannabis use profiles, depending on continuity and frequency of cannabis use following onset. Type of cannabis (hash-like vs. skunk-like) used was assessed by asking subjects to describe their preferred type of cannabis. Based on this information, grouping was done in the same fashion as reported previously (Di Forti, Marconi, et al., 2015), and consistent with previous reports on the characteristics of the cannabis samples seized by the police in London (Potter et al., 2008).

Information regarding service use, number, duration and legal status (voluntary/involuntary) of in-patient admissions, referral to crisis intervention team or standard treatment by a community mental health team was obtained from electronic patient records. Data was extracted using the WHO Life Chart Schedule (Susser et al., 2000b), which allows prospective recording of the course of illness in terms of treatment history. As the main outcome measure, relapse was defined as admission to a psychiatric inpatient unit owing to exacerbation of psychotic symptoms within two years following first presentation to psychiatric services and receiving a diagnosis of psychosis. If the patient was hospitalized at their first presentation to psychiatric services with a diagnosis of psychosis, this was not considered as a relapse event. All patients received care from a specialized Early Intervention community team for Psychosis.

Alcohol use, other illicit drug use and cigarette use, illness severity at onset (indexed as onset care intensity) and medication adherence were assessed and included in the analysis as potential confounders based on previous literature. Measurements of

cannabis use, relapse and confounders estimated are described in *Table 15*. (below). Demographic and clinical information recorded at onset were used to compare the different cannabis use groups in terms of family history of mental illness [diagnosis of axis I psychiatric illness in at least one first degree relative], ICD10 diagnosis [affective vs. non-affective psychosis (based on ICD-10 diagnosis assessed with OPCRIT (McGuffin, Farmer, & Harvey, 1991))] and employment status [employed=in full-time or part-time employment, self-employed; unemployed = not employed, economically inactive, student]. Several covariates were assessed and included in the analysis (cf. *Table 18.*) as potential confounders based on previous literature [cf. Olivares et al. (2013)].

Table 15. Study variables

Cannabis profile (categorical variable)	
0: Former (regular) user	Subject who had a history of regular cannabis use (defined as use at least once/month for 6 consecutive months) prior to their onset but who used cannabis only infrequently (< 6 times) in the two years following the onset of psychosis.
1: Never (regular) user	Subjects who were never regular users of cannabis either prior to (less than once/month for 6 consecutive months) or following (< 6 times over the follow-up period) the onset of psychosis.
2: Post-onset intermittent user	Subjects who used cannabis more than infrequently (> 6 times) following the onset of psychosis but not consistently every month over the first two years following the onset of illness.
3: Post-onset continued user – hash-like	Subjects who used low-potency cannabis ("hash-like" like hash, resin) [cf. Di Forti, Marconi, et al. (2015) for classification] continuously (defined as use at least once in each month of the years following the onset).
4: Post-onset continued user – skunk-like (low-frequency)	Subjects who used l high-potency cannabis ("skunk-like") [grouping was done in the same fashion as reported previously(Di Forti, Marconi, et al., 2015), and consistent with previous reports on the characteristics of the cannabis samples seized by the police in London(Potter et al., 2008).] continuously (defined as use at least once in each month of the years following the onset) but in a low-frequency manner (less than daily).
5: Post-onset continued user – skunk-like (high-frequency)	Subjects who used high-potency cannabis ("skunk-like") [cf. row above for classification] continuously in a high-frequency manner (daily use).
Relapse definition	
Risk of relapse	Relapse (yes/no) of psychosis was coded as 'yes' if a patient was admitted to a psychiatric inpatient unit at least once following the onset of illness over the two ensuing years. Any hospital admission that was part of the first episode was not included as a relapse.
Number of relapses	Number of relapses was calculated as a continuous variable by estimating the cumulative number of hospital admissions following the onset of illness over the 2 year period.
Length of relapse	Length of relapse was calculated by estimating the cumulative number of months spent in hospital over the two years following the onset of illness. The time spent in hospital as part of the first episode was not included in this measure.
Time to first relapse	Time to first relapse was measured as the consecutive number of survival months without experiencing a relapse. Those subjects who did not relapse following the onset were allocated a survival time of 24 months.
Care intensity at follow-up	This outcome was computed as an ordinal variable by rating each subject's intensity of service use within two years following the onset [0=Required only community treatment without crisis intervention; 1=Required crisis intervention without hospital admission; 2= Required hospital admission

	without compulsory admission; 3=Required compulsory hospital admission (admitted under section 2, section 3, section 136, through crown and magistrates (Section 35, 36, 37, 41 & 48), section 4 or section 5 if converted to sec 2 or 3 subsequently)].
Confounders	
Alcohol use	Alcohol use (yes/no) since onset derived from CEQ_{mv} . Similar to previous ratings (Faber et al., 2012), subjects were considered as users if they had a history of daily use for at least one month within the two years following the onset of illness.
Other illicit drug use	Other illicit drug use (yes/no) derived from the CEQ_{mv}. Subjects were considered as users if they had consumed illicit drugs recreationally ($\geq$ 6 times) within the two years following the onset of illness. The cut-off used was comparable to previous studies (e.g.González-Pinto et al. (2011), which used < 4 times used in the previous year as the cut-off for non-regular user).
Cigarette use	Cigarette use data was collected using the CEQ_{mv}. Subjects were considered as smokers if they consumed cigarettes regularly ($\geq$ 365 days of use) within the two years following the onset of illness.
Care intensity at onset	Care intensity at onset was computed as an ordinal variable by rating each subject's intensity of service use at onset (cf. coded as above for care intensity at follow up). In order to arrive at a measure reflective of onset illness severity, I included this predictor as a continuous variable (range 0-3) in all multiple regression models.
Medication adherence	Similar to previous reports (Faridi et al., 2012), medication adherence was dichotomized (adherence vs. non-adherence), rating a patient's adherence as compliant if the prescribed medication was taken regularly for more than 34% of the time within the two years following the onset of illness.
Other	Other covariates included gender (male/female), ethnicity (white/non-white), age of onset of psychosis (age at first presentation to the psychiatric services for psychosis)

4.3.3 DATA ANALYSIS

Data analysis was performed using R (Bossong et al., 2013). Follow-up data for a fixed two-year period following onset of psychosis was modeled for every subject. The cannabis profile variable was coded as an ordered categorical variable (cf. *Table 15.*), with the former (regular) user group acting as the reference group. I chose the former user group as reference because it allowed us to account to a substantial extent for the effect of any putative shared stable vulnerability factors (such as genetic vulnerability) (Schoeler, Murray, et al., 2016) that have been argued to underlie the association between cannabis use and psychosis relapse (Ksir & Hart, 2016b) as both the continued cannabis user groups and the former user group would have been affected by common shared stable vulnerability factors. The argument that cannabis-using patients with psychosis may represent a neurodevelopmentally distinct subgroup compared to never using psychosis patients (Schoeler, Kambeitz, et al., 2016; Murat Yücel et al., 2012), also makes the former cannabis user group a better choice. Clinically as well, they are the most meaningful comparison group because they are the discontinued users as opposed to continuing users.

First, exploratory simple analyses, including chi-square (χ^2) test for categorical variables and Kruskal-Wallis test and Mann-Whitney U (two-sided) test for continuous outcomes were used to compare the different cannabis use groups for continuous outcomes (number of relapses, length of relapse, time to relapse, care intensity at follow up). This non-parametric test was chosen as the Shapiro-Wilk Normality Test statistic was highly significant for those outcomes ($p<0.001$). Following common practice (Stepniak et al., 2014), I generated Kaplan-Meier curves and compared the different cannabis use groups using log-rank tests. Pairwise comparisons were adjusted using Bonferroni correction to account for multiple testing.

Second, to test the hypothesis whether the different cannabis use groups were significantly different to the former (regular) user group in their relapse outcome, I employed multiple regression models to test whether the categorical cannabis use variable predicted outcome after controlling for confounders. Antipsychotic medication adherence was included in a separate regression model on its own as this data was only available for a subset of cases, considering that antipsychotic medications were not prescribed for all subjects following the onset of illness. Multiple logistic regression analyses were employed to compute the odds ratio (OR) and 95% CIs, using binary logistic regression for binary outcomes (risk of relapse) and ordinal logistic regression analysis for ordered categorical outcome (care intensity at follow-up). Multiple negative binominal regression models were employed for continuous outcomes (number of relapses, length of relapse, time to relapse). This regression analysis was preferred over Poisson regression since there was evidence of over-dispersion for the outcome variables (i.e. the conditional variance was higher than the conditional mean). As there was an excess of zero observations for count data (number of relapses), I tested whether a zero-inflated negative binominal regression model (ZINB) was a better fit for the data compared to a negative binominal regression model, which it was not, and hence not considered (Vuong $p \geq 0.05$). Sensitivity analysis was performed by calculating propensity scores (PS) in order to validate the results and to address the limitations by confounding adjustment in regression analysis (Rubin, 2001). PS was defined as the patients' probability of being classified as one of the treatment groups [never (regular) user; post-onset intermittent user; post-onset intermittent user; post-onset continued user – hash-like; post-onset continued user – skunk-like (low frequency); post-onset continued user – skunk-like (high frequency)] versus the control group (former regular users), based on their individual observed covariates. Probability was estimated using a

multiple logistic regression model with the dichotomized (treatment vs. control) variable as the dependent variable, which included all covariates as specified in *Table 15*. The treatment group was matched to controls by PS using an optimal nearest neighbourhood-matching algorithm. The balance of all covariates among the treatment group and their PS-matched controls was checked using the *p*-value estimates from logistic regression analysis (cf. *aTable 7.*, Appendix III) before carrying out the sensitivity analysis in the matched sample.

4.4 RESULTS

4.4.1 SAMPLE CHARACTERISTICS

Two hundred fifty-six FEP patients took part in this study. Majority of patients (78.1%) were admitted to hospital around the onset of illness; over half of those (59.5%) experienced involuntary admission. Within the first 2 years following onset of illness, 36.3% of patients experienced a relapse leading to hospital admission. Three relapses within the two years following the onset was the maximum number of relapses that occurred in this sample, while the longest time spent in hospital was 14.8 months. Out of N=153 subjects with pre and/or post-onset regular cannabis use, only n=2 (1.3%) subjects started using cannabis following onset (with no previous history of regular use), while n=97 (63.4 %) had used cannabis regularly prior to onset and used it subsequently either intermittently or continuously and n=54 (35.3%) had a history of regular use prior to onset but did not use it regularly following onset. 24.6% (n=63) of the patients had never tried cannabis in their lifetime. Use of other illicit drugs was reported by n=27 (10.5%) in the two years following onset of psychosis. In this group, n=19 (70.4%) used cocaine, n=8 (29.6%) used opioids, n=8 (29.6%) used amphetamines, n=3 (11.1%) used hallucinogens, n=2 (7.4%) used poppers and n=1 (3.7%) used ketamine following the onset. On comparing the different groups based on their cannabis use patterns it appeared that they significantly (Kruskal-Wallis, p=0.02) differed in the age of onset of their psychosis, with continued cannabis users comprising the group with the youngest age of onset. The cannabis user groups as shown in *Table 16.* did not differ with regard to the proportion of patients taking antipsychotic medication (χ^2=0.93, p=0.82), the type of antipsychotic medication prescribed at onset (first-generation vs. second-generation antipsychotics) (χ^2=2.61, p=0.46) or their ICD-10 psychosis diagnosis at onset (affective vs. non-affective) (χ^2=1.68, p=0.64). They

also did not differ significantly in their employment status at onset (χ^2=5.24, p=0.15.) or family history of mental illness (χ^2=1.84, p=0.61). Non-white ethnicity was significantly associated with risk of relapse (χ^2=6.46, p=0.01), while type of antipsychotic medication (first-generation vs. second-generation antipsychotics) (χ^2=0.31, p=0.46), non-prescription of antipsychotic treatment (χ^2=0.19, p=0.66), type of psychosis (affective versus non-affective psychosis) (χ^2=0.64, p=0.42), employment status (χ^2=0.37, p=0.54), family history of mental illness (χ^2=0.70, p=0.58), gender (χ^2=0.20, p=0.66) and age of onset (Mann-Whitney U, p=0.38) were not significantly associated with relapse.

Table 16. Sample characteristics

Demographic information	All subjects	Former (regular) user	Never (regular) user	Intermittent user	Continued user	*p* [a]
Number of subjects	256 (100%)	54 (21.1%)	103 (40%)	35 (13.7%)	64 (25%)	
Age of onset (M/SD)	28.06 (8.03)	28.05 (7.65)	29.74 (8.96)	27.95 (8.21)	25.43 (5.83)	0.02
Gender (n male)	156 (60.9%)	37 (68.5%)	44 (42.7%)	24 (68.6%)	51 (79.7%)	<0.0001
Ethnicity (non-white)	170 (66.4%)	23 (42.6%)	78 (75.7%)	22 (62.9%)	47 (73.4%)	0.0002
Care intensity at onset (n)						0.71
Referral to community team only	39 (15.2%)	12 (22.2%)	15 (14.6%)	4 (11.4%)	8 (12.5%)	
Required contact with crisis team	17 (6.6%)	5 (9.3%)	6 (5.8%)	2 (5.7%)	4 (6.2%)	
Required hospital admission (non-compulsory)	81 (31.6%)	13 (24.1%)	38 (36.9%)	12 (34.3%)	18 (28.1%)	
Required hospital admission (compulsory)	119 (46.5%)	24 (44.4%)	44 (42.7%)	17 (48.6%)	34 (53.1%)	
Months stayed in hospital at onset (M/SD)	1.72 (3.37)	2.10 (6.28)	1.57 (2.09)	1.31 (1.20)	1.88 (2.16)	0.57
Employment status at onset (n in employment)[b]	83 (32.8%)	21 (40.4%)	38 (36.9)%	9 (25.7%)	15 (23.8%)	0.15
Family history of mental illness (n yes)[c]	96 (49%)	20 (44.4%)	40 (54.8%)	11 (42.3%)	25 (48.1%)	0.61
Onset diagnosis (non-affective)	211 (82.4%)	47 (87%)	82 (79.6%)	30 (85.7%)	52 (81.2%)	0.64
Medication prescribed at onset (n yes)	240 (93.8%)	52 (96.3%)	96 (93.2%)	33 (94.3%)	59 (92.2%)	0.82
Type of medication at onset (n)						0.46
Second-generation antipsychotic	236 (98.3%)	52 (100%)	94 (97.9%)	33 (100%)	57 (96.6%)	
First-generation antipsychotic	4 (1.7%)	0 (0%)	2 (2.1%)	0 (0%)	2 (3.4%)	

Note. M=Mean; n=number of subjects; SD=Standard Deviation.

[a] *p*-value estimates from Kruskal-Wallis test for means and Chi-square tests for independence for percentages to compare all cannabis groups

[b]Missing data for n=3

[c]Data available for n=196

4.4.2 CANNABIS USE PROFILES AND RELAPSE OUTCOME: UNADJUSTED ANALYSIS

Risk of relapse was significantly different across all groups (χ^2=15.33, p=0.009). The greatest risk was present in continued high-frequency users of high-potency cannabis ("skunk-like"), while it was lowest in former cannabis users (58.1% vs. 24.1%) currently abstaining. Former cannabis users had the highest rate of community treatment only, requiring no referral for crisis intervention or inpatient care (cf. *Table 17.*). In contrast, low/high-frequency users of high-potency ("skunk-like") were more likely to experience compulsory admissions than former cannabis users (29%/37.5% vs. 7.4%). As shown in *Table 17.*, there was a significant effect of pattern of cannabis use on total number of relapses (Kruskal Wallis, p=0.01), length of relapses (Kruskal Wallis, p=0.009), time to relapse (Kruskal Wallis, p=0.02) and care intensity (Kruskal Wallis, p=0.005). Kaplan-Meier curves further indicated that the different groups significantly differed with regard to their time to relapse (Kaplan-Meier p=0.007). More specifically, the user group high-frequency /"skunk-like" user was more likely to experience an earlier relapse than the former (regular) user group (Kaplan-Meier with Bonferroni correction p=0.006, cf. *Figure 15.* below).

Table 17. Cannabis use pattern and relapse outcome

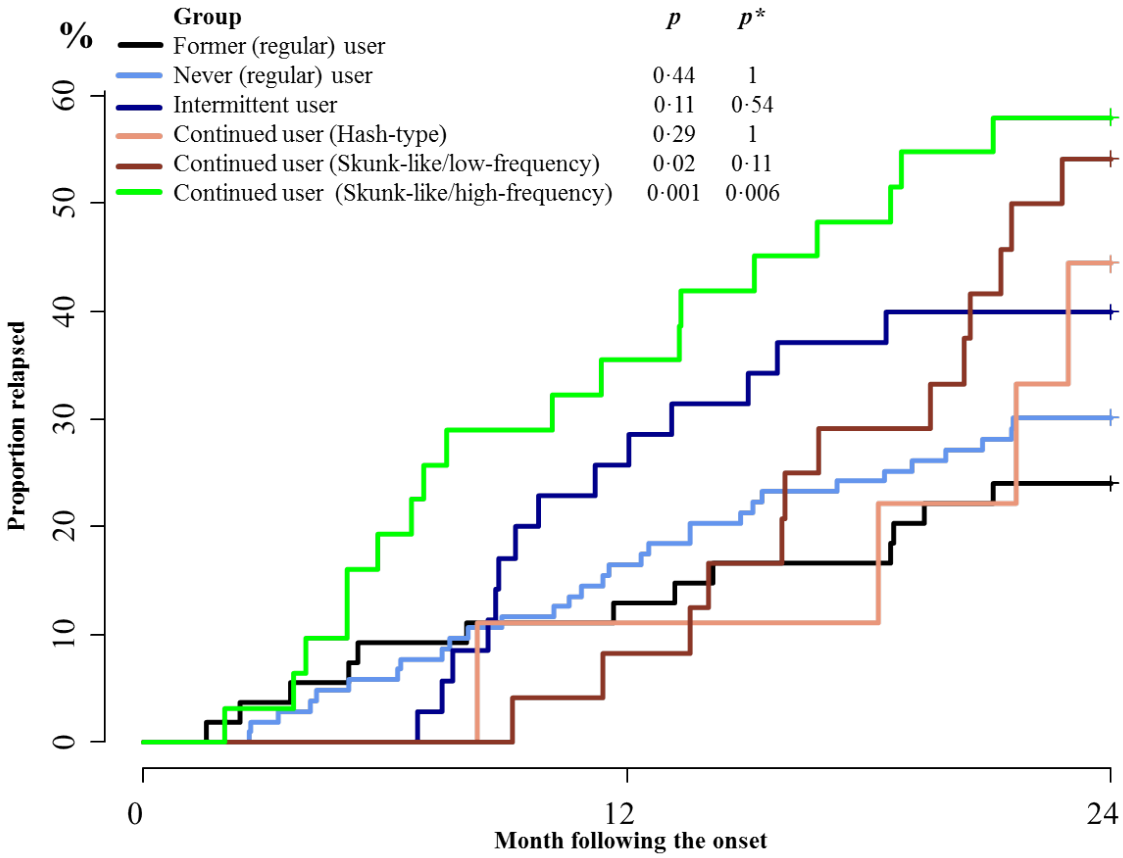
	Relapse (yes) (n/%)[a]	Number of relapses M(SD)[b]	Length of relapses M(SD)[b]	Time to relapse M(SD)[b]	Care intensity at follow-up (n/%)[a]			
					0	1	2	3
Former (regular) user	13 (24.1)	0.35 (0.73)	0.59 (1.74)	20.86 (6.55)	40 (74.1)	1 (1.9)	9 (16.7)	4 (7.4)
Never (regular) user	31 (30.1)	0.43 (0.74)	0.66 (1.46)	20.24 (6.57)	59 (57.3)	13 (12.6)	16 (15.5)	15 (14.6)
Intermittent user	14 (40.0)	0.51 (0.70)	1.66 (3.53)	18.75 (6.88)	16 (45.7)	5 (14.3)	4 (11.4)	10 (28.6)
Continued user (Hash-like)	4 (44.4)	0.67 (1.00)	1.11 (2.07)	21.23 (5.22)	5 (55.6)	0 (0.0)	1 (11.1)	3 (33.3)
Continued user (Skunk-like/low frequency)	13 (54.2)	0.62 (0.65)	1.69 (3.34)	20.27 (4.67)	11 (45.8)	0 (0.0)	4 (16.7)	9 (37.5)
Continued user (Skunk-like/high frequency)	18 (58.1)	0.87 (0.92)	1.71 (2.85)	16.03 (8.21)	12 (38.7)	1 (3.2)	9 (29.0)	9 (29.0)

Note. Care intensity at follow-up (0=Required only community treatment without crisis intervention; 1=Required crisis intervention without hospital admission; 2= Required hospital admission without compulsory admission; 3=Required compulsory hospital admission); M=Mean; SD=Standard Deviation.

[a] Chi-square test for independence to compare all groups for risk of relapse (p=0.009, χ^2=15.33) and care intensity at follow up (p=0.004, χ^2=33.49)

[b] Kruskal-Wallis test to compare all groups in number of relapses (p=0.01), length (months) of relapses (p=0.009), time (months) to relapse (p=0.02)

Figure 15. Time until relapse per cannabis group



Note. Kaplan-Meier curves. *p*-values are estimated from the log-rank tests to compare the different groups [reference group = former (regular) user]
*Bonferroni-corrected significance level

4.4.3 Cannabis use profiles and relapse outcome: Multiple regression analyses

In multiple logistic regression analysis, continued high-frequency use of high-potency ("skunk-like") (indexed as at least daily use throughout the follow-up period) remained a significant predictor for relapse [OR=3.28; 95%CI 1.22-9.18], when compared to former users (cf. *Table 18.* below). The effect also remained significant when medication non-adherence was included in the model [OR=2.73; 95% CI 1.02-7.56]. None of the other cannabis groups were significantly different in their risk of

relapse when compared to former users. In those risk models, only three other predictors remained significant, including non-white ethnicity [OR=2.36; 95% CI 1.23-4.69], care intensity at onset [OR=1.37; 95% CI 1.05-1.84] and antipsychotic medication non-adherence [OR=3.25; 95% CI 1.79-6.09] (cf. *Table 18.*). The results from the other multiple regression analyses confirmed that the adverse effects of continued high-frequency "skunk-like" use were also evident on the number of relapses [IRR=1.77; 95% CI 0.96-3.25], time to relapse [*b*= -0.22; 95% CI -0.40-(-0.04)] and a higher care-intensity at follow up [OR=3.16; 95% CI 1.29-8.09], while controlling for the above confounders. Including medication adherence into the model did not substantially change the results, although high-frequency "skunk-like" use remained a significant predictor only for length of relapse in this model [*b*= 0.98; 95% CI 0.09-0.1.90)] (cf. *Table 18.*). In propensity score-matched analyses considering all covariates (cf. *Table 19.*), the effect of high-frequency "skunk-like" use was reduced in its magnitude but remained a significant predictor for risk of relapse [56.7% vs. 30%, OR=3.05; 95% CI 1.08-9.15] and care intensity at follow up [OR= 3.18; 95% CI 1.19-8.97].

Table 18. Cannabis use pattern and relapse outcome: Multiple regression analyses

	Risk of relapse			**Number of relapses**			**Length of relapse**			**Time to relapse**			**Care intensity at follow-up**		
Model 1 (N=256)	*OR*[a]	*95% CI*	*p*	*IRR*[b]	*95% CI*	*p*	*b*[c]	*95% CI*	*p*	*b*[c]	*95% CI*	*p*	*OR*[d]	*95% CI*	*p*
Never (regular) user	1.24	0.53-3.03	0.63	1.27	0.70-2.29	0.43	-0.01	-0.81-0.79	0.99	-0.01	-0.15-0.13	0.92	2.01	0.91-4.60	0.09
Intermittent user	1.76	0.67-4.64	0.25	1.22	0.64-2.34	0.54	0.78	-0.09-1.66	0.07	-0.06	-0.23-0.10	0.46	2.78	1.14-6.91	**0.03**
Continued user (Hash-like)	1.82	0.36-8.76	0.45	1.13	0.43-2.97	0.80	-0.33	-1.84-1.25	0.65	0.07	-0.20-0.35	0.60	2.40	0.51-10.44	0.25
Continued user (Skunk-like/low frequency)	2.42	0.80-7.52	0.12	1.11	0.54-2.31	0.77	0.41	-0.64-1.49	0.41	0.05	-0.14-0.25	0.60	3.12	1.09-9.08	**0.03**
Continued user (Skunk-like/high frequency)	3.28	1.22-9.18	**0.02**	1.77	0.96-3.25	0.07	0.61	-0.31-1.55	0.17	-0.22	-0.40-(-0.04)	**0.02**	3.16	1.26-8.09	**0.01**
Ethnicity (non-white)	2.36	1.23-4.69	**0.01**	1.82	1.16-2.85	**0.01**	0.97	0.35-1.59	**0.002**	-0.12	-0.23-(-0.01)	**0.03**	1.94	1.08-3.54	**0.03**
Gender (Female)	1.42	0.78-2.60	0.26	1.20	0.82-1.74	0.35	-0.27	-0.83-0.30	0.33	-0.04	-0.14-0.06	0.44	1.51	0.88-2.61	0.13
Other illicit drug use	1.79	0.68-4.76	0.24	1.79	1.05-3.04	**0.03**	0.70	-0.17-1.60	0.10	-0.11	-0.28-0.07	0.23	1.43	0.60-3.41	0.42
Cigarette use	1.49	0.78-2.83	0.23	1.73	1.12-2.67	**0.01**	0.37	-0.17-0.92	0.20	-0.07	-0.18-0.04	0.24	1.66	0.92-3.02	0.09
Age of onset	1.01	0.97-1.04	0.78	1.00	0.97-1.02	0.82	-0.02	-0.05-0.01	0.30	0.00	-0.01-0.00	0.42	0.99	0.96-1.03	0.71
Alcohol use	1.72	0.75-3.94	0.20	1.14	0.69-1.88	0.60	-0.09	-0.85-0.69	0.81	-0.01	-0.15-0.14	0.90	1.96	0.95-4.08	0.07
Care intensity at onset	1.37	1.05-1.84	**0.03**	1.32	1.08-1.60	**0.01**	0.59	0.32-0.87	**<0.001**	-0.03	-0.07-0.02	0.22	1.33	1.03-1.73	**0.03**

Table 18. Cannabis use pattern and relapse outcome: Multiple regression analyses (cont'd)

	Risk of relapse			**Number of relapses**			**Length of relapse**			**Time to relapse**			**Care intensity at follow-up**		
Model 2 (N=236)	*OR*[a]	*95% CI*	*p*	*IRR*[b]	*95% CI*	*p*	*b*[c]	*95% CI*	*p*	*b*[c]	*95% CI*	*p*	*OR*[d]	*95% CI*	*p*
Never (regular) user	1.28	0.58-2.88	0.55	1.13	0.65-1.98	0.65	0.20	-0.55-0.94	0.59	-0.01	-0.15-0.12	0.83	1.80	0.88-3.86	0.12
Intermittent use	1.57	0.58-4.29	0.37	1.22	0.62-2.42	0.56	0.78	-0.14-1.74	0.09	-0.06	-0.23-0.12	0.53	2.47	1.00-6.20	**0.05**
Continued user (Hash-like)	2.54	0.50-12.98	0.25	1.74	0.67-4.52	0.25	0.57	-0.80-2.23	0.45	0.04	-0.25-0.33	0.80	3.30	0.70-14.76	0.12
Continued user (Skunk-like/low frequency)	2.63	0.91-7.91	0.08	1.34	0.66-2.7	0.42	0.89	-0.06-1.91	0.08	0.03	-0.16-0.23	0.74	3.23	1.17-9.07	**0.02**
Continued user (Skunk-like/high frequency)	2.73	1.02-7.56	**0.05**	1.74	0.94-3.24	0.08	0.98	0.09-1.90	**0.04**	-0.20	-0.38-(-0.01)	**0.03**	2.93	1.17-7.47	**0.02**
Medication non-adherence	3.25	1.79-6.09	**<0.001**	2.29	1.46-3.57	**<0.001**	0.57	-0.01-1.15	**0.05**	-0.15	-0.25-(-0.05)	**0.01**	3.36	1.93-6.00	**<0.001**

Note. Reference group = Former (regular) users

[a] *OR* = Odds Ratio estimates from multiple logistic regression analysis

[b] *IRR* = Incidence Rate Ratio estimated from negative binomial regression

[c] *b* = Coefficient estimate from negative binomial regression

[d] *OR* = Odds Ratio estimates from multiple ordinal regression analysis

Table 19. Sensitivity Analysis (Propensity Score Matching)

Outcome	Matched (n=68)				Matched (n=62)				Matched (n=16)				Matched (n=46)				Matched (n=60)			
Relapse (yes): n (%)	*FC*	*NC*	*OR*[a]	*p*	*FC*	*IC*	*OR*[a]	*p*	*FC*	*CC-H*	*OR*[a]	*p*	*FC*	*CC-SL*	*OR*[a]	*p*	*FC*	*CC-SH*	*OR*[a]	*p*
	9 (73.5)	9 (73.5)	1.00 (0.34-2.97)	1.00	9 (29)	12 (38.7)	1.54 (0.54-4.56)	0.42	2 (25)	4 (50)	3.00 (0.38-30.47)	0.31	8 (34.8)	13 (56.5)	2.44 (0.75-8.31)	0.14	9 (30)	17 (56.7)	3.05 (1.08-9.15)	**0.04**
Number of relapses: M(SD)	*FC*	*NC*	*IRR*[b]	*p*	*FC*	*IC*	*IRR*[b]	*p*	*FC*	*CC-H*	*IRR*[b]	*p*	*FC*	*CC-SL*	*IRR*[b]	*p*	*FC*	*CC-SH*	*IRR*[b]	*p*
	0.44 (0.86)	0.38 (0.70)	0.87 (0.33-2.24)	0.77	0.48 (0.89)	1.07 (0.72)	0.06 (0.47-2.43)	0.88	0.25 (0.46)	0.75 (1.04)	3.00 (0.57-15.70)	0.19	0.52 (0.85)	0.65 (0.65)	1.25 (0.59 -2.67)	0.57	0.47 (0.86)	0.83 (0.91)	1.79 (0.88-3.63)	0.11
Length of relapse: M(SD)	*FC*	*NC*	*b*[c]	*p*	*FC*	*IC*	*b*[c]	*p*	*FC*	*CC-H*	*b*[c]	*p*	*FC*	*CC-SL*	*b*[c]	*p*	*FC*	*CC-SH*	*b*[c]	*p*
	0.80 (2.14)	0.67 (1.60)	-0.17 (-1.43-1.08)	0.79	0.82 (2.20)	1.16 (2.79)	0.35 (-0.80-1.51)	0.54	0.17 (0.37)	1.25 (2.17)	1.98 (0.03-4.55)	0.07	1.11 (2.54)	1.76 (3.40)	0.46 (-0.67-1.60)	0.42	0.87 (2.25)	1.74 (2.90)	0.69 (-0.27-1.66)	0.16
Time to relapse	*FC*	*NC*	*b*[c]	*p*	*FC*	*IC*	*b*[c]	*p*	*FC*	*CC-H*	*b*[c]	*p*	*FC*	*CC-SL*	*b*[c]	*p*	*FC*	*CC-SH*	*b*[c]	*p*
	20.49 (7.06)	21.21 (5.46)	0.03 (-0.13-0.20)	0.69	19.68 (7.45)	19.03 (6.75)	-0.03 (-0.24-0.18)	0.75	20.76 (6.21)	20.89 (5.47)	0.01 (-0.27-0.28)	0.98	19.81 (6.81)	20.11 (4.70)	0.02 (-0.17-0.20)	0.87	20.11 (6.90)	16.01 (8.35)	-0.23 (-0.48-0.03)	0.08
Care intensity at follow-up[d]	*OR*[b] *(NC vs. FC)*			*p*	*OR*[b] *(NC vs. IC)*			*p*	*OR*[b] *(NC vs. CC-H)*			*p*	*OR*[b] *(NC vs. CC-SL)*			*p*	*OR*[b] *(NC vs. CC-SH)*			*p*
	1.83 (0.66-5.31)			0.25	2.37 (0.90-6.52)			0.09	3.26 (0.44-31.93)			0.26	2.88 (0.93-9.39)			0.07	3.18 (1.19-8.97)			**0.02**

Note. Cannabis profiles [FC = Former (regular) cannabis user; Never (regular) cannabis user; IC = Intermittent cannabis user; CC-H: Continued cannabis user (Hash-like); CC-SL = Continued cannabis user (Skunk-like/low frequency); CC-SH = Continued cannabis user (Skunk-like/high frequency)].

[a] OR = Odds Ratio (95% Confidence Interval) estimates from multiple logistic regression analysis

[b] IRR = Incidence Rate Ratio (95% Confidence Interval) estimated from negative binomial regression

[c] *b* = Coefficient estimate from negative binomial regression

[d] *OR* = Odds Ratio estimates from multiple ordinal regression analysis

As shown in *Table 18*., several other predictors were significantly linked to relapse in the multiple regression analyses. Ethnicity and medication non-adherence remained a significant predictor in all models, including risk of relapse, number and length of relapses, time to relapse and care intensity at follow up. Number of relapses was predicted by cigarette use [IRR=1.73; 95% CI 1.12-2.67] and other illicit drug use [IRR=1. 79; 95% CI 1.05-3.04]. Finally, higher care intensity at onset was associated with risk of relapse [OR=1.37, 95% CI 1.05-1.84], an increase in number of relapses [IRR=1.32; 95% CI 1.08-1.60] and increase of length of relapse [*b*=0.59; 95% CI 0.32-0.87], as well as a higher care intensity throughout the two years following the onset of illness [OR=1.33; 95% CI 1.03-1.73]. Further analyses with the continued user group (skunk-like/high-frequency) as the reference group additionally indicated that this group relapsed earlier when compared to continued user (hash-like) [*b*=0.29; 95% CI 0.01-0.58] and continued user (Skunk-like/low frequency) [*b*=0.27 95% CI 0.06-0.48] as well as never (regular) user [*b*=0.21 95% CI 0.04-0.39] groups (a*Table 8.,* Appendix III).

4.5 DISCUSSION

For the first time, this study on outcome in FEP was able to investigate the effect of different patterns of cannabis use on risk of relapse in psychosis by incorporating information on continuation, frequency and type of cannabis used. My results indicate that effects of cannabis use on outcome vary depending on specific cannabis use profile. While former regular cannabis users who stopped using the substance regularly following onset of psychosis had the lowest risk of relapse, those who continued to use at least on a monthly basis were most likely to experience a relapse. More specifically, continued users of high-potency cannabis ("skunk-like") who were using on a daily basis had the highest risk of relapse of psychosis (OR 3.28), when compared to former cannabis users. This effect was independent of other putative risk factors for poor outcome, including ethnicity, gender, age of onset, alcohol, cigarette and illicit drug and care intensity at onset. Furthermore, high-frequency "skunk-like" users also had higher number of relapses, longer duration of hospital stay, shorter time to relapse and more severe (as indexed by care intensity at follow up) relapses, when compared to former users. More rigorous adjustment for confounders using propensity score matching showed similar results, with high-frequency "skunk-like" users having a 1.9 times higher risk (57% vs 30%) of relapse of psychosis. This is comparable, albeit in the opposite direction, to the effect of antipsychotic medication treatment on risk of relapse in psychosis [e.g. 2.4 (64% vs 27%) times higher risk for placebo versus drug-treated patients (Stefan Leucht et al., 2012)]. High-frequency "skunk-like" users also relapsed earlier when compared to "hash-like" and low-frequency "skunk-like" continued cannabis users as well as never (regular) users. Together, these results extend previous observational (Bergé et al., 2016; Hides et al., 2006; Stepniak et al., 2014) and experimental evidence (D'Souza et al., 2005) of dose-response effects of cannabis in

patients with psychosis to demonstrate that the effects of cannabis use on outcome in psychosis depend on the type of cannabis consumed as well as frequency of use. This is consistent with similar evidence on the onset of psychosis (Di Forti, Marconi, et al., 2015). High-potency ("skunk-like") cannabis has become dominant in the UK (Hardwick & King, 2008) and is characterized by high levels of delta-9-tetrahydrocannabiniol (THC), the main psychoactive ingredient in cannabis, which may exerts its effects through its impact on the neural substrates implicated in psychosis (Sagnik Bhattacharyya et al., 2012; Sagnik Bhattacharyya et al., 2009). Furthermore, it has minimal concentrations of cannabidiol (CBD) (Hardwick & King, 2008), which has been shown to ameliorate some of the effects of THC (Sagnik Bhattacharyya et al., 2010a) and may have antipsychotic properties (Leweke et al., 2012) and is more present in hash-forms of cannabis (Hardwick & King, 2008). Higher relapse rates and shorter time to relapse in high-frequency skunk users may be the result of a failure to respond to antipsychotic treatment (Patel R et al., 2016) either on its own or in combination with an increase in the severity of psychotic symptoms in those frequently exposed to a higher dose of THC (D'Souza et al., 2005), which were not investigated in the present study. This may explain why some previous studies that did not differentiate between the type of cannabis, may have failed to observe an association between cannabis use and relapse (Baeza et al., 2009; Faber et al., 2012). This may also explain why the risk estimate observed in our study for the high-dose group (high-frequency/skunk-like) was substantially higher when compared to the pooled odds from previous studies that investigated the risk of cannabis on relapse [OR_{simple} 4.37 vs. OR_{simple} 1.97] (Schoeler, Monk, et al., 2016). Interestingly, the cannabis users who remained abstinent following the onset of psychosis (35%) did not differ from the non-user group with regard to outcome. This would imply that the effects of previous cannabis use on outcome in

psychosis are not irreversible (Schoeler, Monk, et al., 2016) and suggest a need to move beyond investigations of the effects of lifetime cannabis use or cannabis use assessed at onset only (Manrique-Garcia et al., 2014c; Wunderink et al., 2009). Considering the variable course of cannabis use following the onset of psychosis, future investigations should therefore focus on changes in pattern of use and type of cannabis used following psychosis onset, since the specific pattern of use as well as type of cannabis used may be the key factors driving adverse outcomes associated with cannabis use in psychosis.

Consistent with previous reports (Caseiro et al., 2012; Leeson et al., 2012), cannabis users were less likely to be adherent to antipsychotic medication and non-adherence remained the strongest predictor for relapse in our sample. The reduced magnitude of the effect of cannabis on risk of relapse when medication non-adherence was included in the multiple model [from OR_{simple} 4.37 (95% CI 1.72-11.85) to $OR_{multiple}$ 2.73 (95% CI 1.02-7.56)] suggest that some of the effects of cannabis on outcome may perhaps relate to its association with non-adherence to antipsychotic medication. Nevertheless, similar to experimental evidence (D'Souza et al., 2005) and studies that reported reduced but significant adverse effects of cannabis in adherent patients on relapse and symptomatic outcome (Faridi et al., 2012; Hides et al., 2006; Sorbara et al., 2003), my data suggest that high-frequency use of potent forms of cannabis will adversely affect outcome even in adherent patients. This is consistent with evidence that cannabis use may reduce the effectiveness of antipsychotic treatment (Patel R et al., 2016). In line with independent evidence (Schaub, Fanghaenel, & Stohler, 2008), my results are also not in favour of the notion that the adverse outcomes seen in cannabis users were a result of self-medication due to a more severe psychopathology, since higher intensity of care at onset did not confound the effect and one would then expect a similar association between cannabis use and outcome in

ongoing users of hash-like cannabis, which was not present. Other illicit drug or cigarette use were only associated with the number of relapses but none of the other outcomes suggesting that this effect may reflect their common association with cannabis use. However, I did not investigate dose-response relationships for cigarette use and other drug use as I did with cannabis use patterns. Finally, my finding that black ethnicity remained a significant and consistent predictor for all outcomes is in line with previous reports of its association with poor outcome in psychosis in the UK (N. Goater et al., 1999).

In summary, my results are opposed to a non-causal explanation for the association between cannabis use and outcome, such as reverse causation or confounding and indicate that change in cannabis use following onset in an important determinant for outcome in psychosis. I was able to show an increased risk of relapse in patients who continued with their cannabis use in a pattern that involved frequent (daily) use of high-potency ("skunk-like") forms, when compared to former cannabis users. Previous RCTs have failed to effectively diminish cannabis use in patients with psychosis [e.g.C. Barrowclough et al. (2014)]. Furthermore, there is a lack of effective pharmacological treatments that can help treat comorbid cannabis use (Wilson & Bhattacharyya, 2016) in patients with psychosis, highlighting a need for effective interventions. Our results suggest that reducing frequency of use or shifting to less potent forms may be potentially useful intervention strategies in psychotic patients who are otherwise unable to stop using cannabis.

This study has certain limitations that need to be outlined. First, cannabis and other substance use following onset were assessed retrospectively using self-report based measures and are therefore subject to under-reporting. However, interview data were validated by screening clinical notes and comparison of data on premorbid

cannabis use collected at onset of illness and again at follow-up revealed high concordance, suggesting minimal risk of under-reporting. Lack of objective measurement of cannabis use by screening hair or urine samples may have resulted in under-reporting of cannabis use. While this may have resulted in underestimation of the effect of cannabis use on outcome, it is unlikely to have affected the general direction of results reported herein. Furthermore, underreporting of cannabis use has been found to be less of an issue in research studies, when self-report data on cannabis use has been compared to objective measures such as urine drug screen (Di Forti et al., 2012). Few subjects (n=8) in the continued hash(resin)-user group may have undermined our ability to detect harm related to ongoing hash use. Also, I did not separately investigate those who started using cannabis following the onset of psychosis but had no history of premorbid regular use, as only two subjects fell into this category. It may be argued that I did not control for the effect of migrant status, which may have confounded the results of our study, as migrant status may be associated with a worse outcome. However, I did in fact control for the effect of ethnicity, and the main results presented here survive after controlling for ethnicity. While it is true that our measure of ethnicity does not reflect an accurate measure of migration status, the non-white ethnic group is still likely to capture a majority of the first-generation migrants (Coid et al., 2008) and thus account for a substantial proportion of any confounding effect of migrant status on relapse. Furthermore, in a subset-analysis (n=86) in the white ethnic group, I compared non-British (i.e. those who are likely to have migrated) white ethnic subjects to British subjects. The results indicate that there was no difference between the two groups with regard to risk of relapse (23% vs. 32%, χ^2= 0.72, p=0.38). This is also consistent with independent evidence that in FEP patients, migration status was not linked to the number of hospitalisations in a 2-year follow up (Abdel-Baki et al., 2015). Hence, it is

unlikely that this would have affected the conclusions of the present study. Another potential caveat worth considering is the effect of type and dose of antipsychotic medication on relapse. While type of antipsychotic medication prescribed did not differ between the different cannabis user groups examined, nor was it related to relapse of psychosis, I could not test the effect of dose of antipsychotics prescribed as this data was not available. However, I do not think that this would have substantially affected the results of the present study as antipsychotic dose titration was carried out by consultant psychiatrists who were independent of the research team and blind to the specific hypotheses examined in the present study, making it highly unlikely that antipsychotic dosing would have been systematically associated with the cannabis use status of patients rather than their symptom status, response to antipsychotics and tolerability of dose prescribed. Perhaps the more important potential confounder that is relevant is adherence to antipsychotic medications, which I have taken into consideration.

As in any longitudinal study, I cannot rule out that this sample may comprise a selective subset of inner city FEP patients who were more likely to engage with community mental health services and suffer from less severe psychopathology. However, this is unlikely to have affected the conclusions of the present study as engagement and recruitment of patients with more severe psychopathology was unlikely to have been systematically better in those with a comorbid cannabis use history. Finally, those who refused to take part in the follow-up were excluded from the analysis as relevant data was missing for them. It is possible that refusal to take part in the follow-up study may in part be directly related to their cannabis use over the follow-up period and also to their course of illness, which may have biased the results of the study. High rates of attrition such as that observed here is a particular problem that is inherent

with observational studies that follow up large cohorts of patients with psychiatric conditions such as the one reported here. While it is not possible to satisfactorily address this limitation in the absence of information about the main predictor of interest, i.e., cannabis use over the follow-up period, I have compared those who participated in the follow-up with those who refused on several baseline measures, including premorbid cannabis use, age of onset of psychosis, ethnicity and gender and the main outcome measure (relapse within 2 years following the onset). These comparisons suggest that those who participated did not differ from those who refused to take part in the follow-up on these measures as well as on the risk of relapse over the 2-year follow-up period. However, I cannot completely rule out the possibility that missing data from those who refused to take part in follow-up may have still biased the results of the present study.

Nevertheless, this is the first study that suggests that those who continue to use high-potency cannabis even after the onset of their psychosis are at the greatest risk of relapse of their illness and of experiencing more frequent and earlier relapses that require more intensive psychiatric care than those who do not continue cannabis use.

5 PAPER 3: EXAMINING THE ASSOCIATION BETWEEN CONTINUED CANNABIS USE AND RISK OF RELAPSE IN FIRST EPISODE PSYCHOSIS: A QUASI-EXPERIMENTAL INVESTIGATION WITHIN AN OBSERVATIONAL STUDY

5.1 ABSTRACT

Background. Cannabis use following a first episode of psychosis (FEP) has been associated with poor outcome, but it is unclear whether this effect is causal in its nature.

Methods. Patients (N=220) presenting to psychiatric services in South London with first episode non-organic [non-affective (ICD10 codes F20-F29) or affective (F30-F33)] psychosis were followed up for at least 2 years following onset of psychosis. Longitudinal modelling was employed (fixed-effects analysis, cross-lagged path analysis) to examine whether the association between changes in cannabis use and risk of relapse over time is the result of shared vulnerability between psychosis and cannabis use, psychosis increasing the risk of cannabis use (reverse causation) or indeed a causal effect of cannabis use on psychosis relapse. I assessed exposure to cannabis within the first and the second year (t1/t2) following onset of psychosis. Relapse of psychosis defined as subsequent hospitalisation for psychosis. Effect of continued cannabis use (C_{t1}/ C_{t2}) and its pattern (CP_{t1}/ CP_{t2}) were modelled for risk of relapse within the first (R_{t1}) and the second year (R_{t2}) following psychosis onset.

Findings. Fixed-effects models adjusting for time-variant (other illicit drug use, antipsychotic medication adherence) and time-invariant unobserved confounders (e.g. genetic/premorbid environment) revealed that there was an increase in odds of experiencing a relapse of psychosis in periods of cannabis use relative to periods of no use (1.13[95% CI 1.03-1.24]). Change in pattern of continuation (CP) significantly increasing the risk (1.07[95% CI 1.02-1.13]), suggesting a dose-dependent relationship.

Cross-lagged analysis confirmed that this association reflected an effect of cannabis use (C_{t1}) on subsequent risk of relapse (R_{t2}) (β =0.44, p=0.04) rather than an effect of relapse (R_{t1}) on subsequent cannabis use (C_{t2}) (β =-0.29, p=0.59).

Interpretation. These results demonstrate a dose-dependent association between change in cannabis use and relapse of psychosis that is unlikely to be a result of self-medication or genetic and environmental confounding.

5.2 INTRODUCTION

Understanding the nature of the association between cannabis use and psychotic disorders is crucial for the formulation of evidence-based health policies concerning cannabis, especially in light of changing public attitudes and legalisation of use in several states in the US as well as in other countries (Lavender, 2016; Reuter, 2010; Scheuer, 2015; Waugh, 2016). This is particularly important because psychotic disorders such as schizophrenia cause the most severe health loss of all human disorders (Whiteford et al., 2013) and are associated with considerable financial burden (Almond et al., 2004; Knapp et al., 2009b) and a very high rate of comorbid abuse of cannabis (Faridi et al., 2012; Johanna Koskinen et al., 2010) , the most commonly used illicit drug worldwide (UNODC, 2015). Cannabis use typically continues following the onset of psychosis and meta-analytic evidence from studies on over 16,500 patients suggest that continued cannabis use following the onset of psychosis is associated with increased relapse rates, length of hospitalisations and psychotic symptom severity (Schoeler, Monk, et al., 2016). However, methodological questions remain (Ksir & Hart, 2016b; Schoeler, Murray, et al., 2016), such as the concern that association between cannabis use and psychotic relapse may reflect the confounding of a shared genetic and environmental risk, or the possibility of reverse causation (Ksir & Hart, 2016b), i.e., psychosis leading to cannabis use rather than cannabis use leading to relapse of psychosis. Studies that have examined the issue of reverse causation in those with pre-existing psychosis report either a bi-directional relationship between cannabis use and symptom severity (Foti et al., 2010), or that frequency of cannabis use predict an increase in subsequent psychotic symptoms, but not vice versa (Degenhardt et al., 2007; Henquet et al., 2010). However, such evidence does not rule out the possibility that systematic differences between cannabis-using and non-using psychotic patients,

such as a genetic predisposition that underlies both psychosis and cannabis use (R. A. Power et al., 2014) may underlie the association between cannabis use and relapse or exacerbation of psychosis. The gold standard of evidence for establishing that cannabis use is causally linked to a risk of relapse in those with pre-existing psychotic disorder would be a placebo-controlled, randomised clinical trial (RCT) involving experimental cannabis administration, which is unlikely to be realized because of ethical reasons. Short of that, a quasi-experimental approach involving the assessment of within-individual changes in cannabis use over time provides a compelling alternative that is considered only second best to RCT when examining causality (J. Murray et al., 2009). The application of such a design, also called fixed-effects analysis of longitudinal panel data (McKetin et al., 2013; Schoeler, Monk, et al., 2016), would allow the control of unobserved time-invariant confounding factors such as shared genetic and environmental factors that do not change over time (Ksir & Hart, 2016b; Schoeler, Murray, et al., 2016) as well as those observed potential confounding factors that change over time. This design has also been employed to factor out all unobserved time-invariant sources of confounding and establish an association between cannabis use and increased risk of psychotic symptoms in the general population (David M Fergusson et al., 2005) and independently in chronic methamphetamine users without a comorbid diagnosis of psychosis (McKetin et al., 2013). Studies (David M Fergusson et al., 2005; J. McGrath et al., 2010; McKetin et al., 2013) also suggest a dose-response relationship between frequency of cannabis use and psychotic symptoms when controlling for pre-exposure confounding factors, an important criteria when establishing causality (A. B. Hill, 1965). While these methodological approaches strengthen the argument for causality and have been employed in investigations conducted in the general population (David M Fergusson et al., 2005), they have not been fully incorporated in studies

investigating the effect of cannabis use on outcome in first episode psychosis (FEP) patients (cf. below *Table 20.*) to systematically address the issues of confounding from shared predisposition, reverse causation and dose-response relationship and establish whether cannabis use can affect outcome of psychosis leading to hospitalisation. Hospitalisation can be reliably measured and objectively compared across studies and has hence been proposed as an ideal outcome measure for RCTs (Burns, 2007) and studies on illness course in FEP (Stefan Leucht et al., 2012). It is also linked to high personal, economic and societal costs (Ascher-Svanum et al., 2010) and therefore remains a major public health concern.

To address the limitations in existing evidence (Matthew Hill, 2015; Ksir & Hart, 2016b) (cf. also *Table 20.* for an overview of studies), I investigated the nature of relationship between continued cannabis use and relapse of psychosis in a large sample of first-episode patients, by:

(1) controlling for unobserved, time-invariant sources of confounding (e.g. genetic profile) and observed time-variant sources of confounding (other illicit drug use, medication adherence) using a fixed-effects analysis approach
(2) employing cross-lagged path analysis to investigate the directionality of the relationship between continued cannabis use and risk of relapse following the onset of psychosis
(3) using two measures of cannabis use, including (i) change in cannabis use status over time (non-user status vs. user status) and (ii) a more detailed measure of cannabis use over the follow-up period that takes into account the pattern of continued cannabis use following onset of illness.

Table 20. Observational studies investigating the temporal relationship between cannabis use and (a) onset of psychosis or (b) outcome in psychosis

Study / Cohort	Study time points (T)	Cannabis measure	Psychosis measure	Analytical design	Findings	Controlled confounders	N	Quality assessment[b]
(a) Population studies investigating cannabis use as a risk factor for onset of psychosis								
David M Fergusson et al. (2005) / New Zealand / General population	t_1: Age 18 t_2: Age 21 t_3: Age 25	C_1: Changes in frequency of cannabis use (t_1-t_3) C_2: Frequency of cannabis use in 12 months prior assessment (t_1-t_3)	P_1: Changes in psychotic symptom severity (SCL) (t_1-t_3) P_2: Psychotic symptom severity (t_1-t_3)	(1) Multiple poisson regression (2) FEM (3) SEM	(1) $C_2 \rightarrow P_2$* (2) $C_1 \rightarrow P_1$* (3) $C_2 \rightarrow P_2$* (3) $P_2 \rightarrow C_2$ (NS)	prior psychotic symptoms, prior cannabis use, other mental disorders, other substance use/alcohol use/cigarette use, stressful life events, deviant peer affiliations	1055	A: (+) B: (+) C: (+) D: (+) E: (+)
Kuepper et al. (2011b)/ Germany / General population	t_1: Age 14-24 (R) t_2: Age 17-27 (R) t_3: Age 26-36 (R)	C_1: Initiation of use between t_1 and t_2 (use $\geq$ 5 times) C_2: Initiation of use between t_2 and t_3 (use $\geq$ 5 times) C_3: Persistence of use (use at t_2 and t_3)	P_1: P2t: Incidence of psychosis between t_2 and t_3 (CIDI) P_2: Persistence of psychosis (presence at t_2 and t_3) P_3: Incidence of psychosis between t_1 and t_2	Multiple logistic regression	$C_1 \rightarrow P_1$* $C_3 \rightarrow P_2$* $P_3 \rightarrow C_1$ (NS)	Age, sex, SES, other drug use, childhood trauma, urbanicity	1923	A: (+) B: (–) C: (+) D: (+) E: (+)
Ferdinand et al. (2005) / Denmark / General population	t_1: Age 4-16 (R) t_2: Age 18-30 (R)	C_1: Initiation of cannabis use prior symptom assessment C_2: Initiation of cannabis use following symptom assessment	P_1: Psychotic symptoms (CIDI) following cannabis use P_2: Psychotic symptoms prior to cannabis use	Cox regression	$C_1 \rightarrow P_1$* $P_2 \rightarrow C_2$*	Age, gender	1580	A: (+) B: (–) C: (+) D: (+) E: (–)
Hélène Verdoux et al. (2003) / France / General population	t: ESM: 1 week, with 5 assessments/day	C_1: Cannabis use prior symptom assessment C_2: Cannabis use following symptom assessment	P_1: Risk of psychotic experience following cannabis use (MINI) P_2: Risk of psychotic experience prior cannabis use	Multilevel regression analysis	$C_1 \rightarrow P_1$* $P_2 \rightarrow C_2$ (NS)	Age, gender, other illicit drug use	79	A: (+) B: (–) C: (+) D: (+) E: (–)

Henquet et al. (2004) / Germany / General population	t_1: Age 14-24 (R) t_2: Age 17-27 (R)	C_1: Cannabis use (yes/no) between t_1 and t_2 ($\geq$ 4 times used) C_2: Cannabis frequency between t_1 and t_2	P_1: Risk of psychosis (CIDI) at t_2 P_2: Psychotic symptoms (CIDI) at t_1	Multiple logistic regression	$C_1 \rightarrow P_1$* $C_2 \rightarrow P_1$* $P_2 \rightarrow C_1$ (NS)	Age, gender, SES, urbanicity, childhood trauma, predisposition for psychosis, tobacco, alcohol and other drug use, baseline cannabis use	2437	A: (+) B: (–) C: (+) D: (+) E: (+)
Henquet et al. (2010) / Netherlands / General population	t: ESM: 6 consecutive days with 12 assessments each day	C_1: Cannabis use prior symptom assessment C_2: Cannabis use following symptom assessment	P_1: Level of psychotic experience following cannabis use P_2: Level of psychotic experience prior cannabis use	Multilevel regression analysis	$C_1 \rightarrow P_1$ (NS) $P_2 \rightarrow C_1$ (NS)	Age, gender, alcohol use and other drug use, level of	38	A: (+) B: (–) C: (+) D: (+) E: (–)
J. McGrath et al. (2010) / Australia / General population	t_1: Age 5 t_2: Age 14 t_3: Age 21	C_1: Duration since first cannabis use C_2: Duration since first cannabis use (following age 15)	P_1: Risk of psychosis (CIDI) P_2: Psychotic symptoms at age 15	Sibling pair analysis, logistic regression	$C_1 \rightarrow P_1$* $P_2 \rightarrow C_2$*	sex, age, parental mental illness, psychotic symptoms at t2	3801	A: (+) B: (+) C: (+) D: (+) E: (–)
McKetin et al. (2013) / Australia/ Methamphetamine abusers	t_1: Age 32 t_2: Age 33 t_3: Age 35	C_1: Changes in frequency of cannabis use (t_1-t_3)	P_1: Presence of psychotic symptoms (BPRS) in 1 months prior assessment	FEM	$C_1 \rightarrow P_1$*	Other drug use	268	A: (+) B: (+) C: (–) D: (–) E: (+)
(b) Prospective studies in patients with psychosis investigating the effects of cannabis use on outcome								
Barrowclough, Gregg, Lobban, Bucci, and Emsley (2015) / UK / Established psychosis with comorbid CUD	t_1: Baseline t_2: 9 months FU t_3: 18 months FU	C_1: Cannabis dose* prior to outcome assessment C_2: Change in cannabis dose* (t_1-t3) * measured based on frequency, type and	P_1: Severity psychotic symptoms (PANSS) following cannabis use P_2: Relapse[a] (yes/no) following cannabis use P_3: Hospital admission (yes/no) following	Multilevel regression analysis	$C_1 \rightarrow P_1$ (NS) $C_1 \rightarrow P_2$ (NS) $C_1 \rightarrow P_3$ (NS) $C_2 \rightarrow P_4$ (NS)	Age, gender, living status, employment, education, SES, DAI, other substance use	110	A: (+) B: (–) C: (+) D: (–) E: (+)

		grams used	cannabis use P_4: Changes in positive symptoms (PANSS) (t1-t3)					
Degenhardt et al. (2007) / Australia / Established psychosis	t_1: Baseline t_2: 1 month FU t_3: 2 months FU t_4: 3 months FU t_5: 4 months FU t_6: 5 months FU t_7: 6 months FU t_8: 7 months FU t_9: 8 months FU t_{10}: 9 months FU t_{11}: 10 months FU	C_1: Frequency of use (number of days per month) prior symptom assessment (t_1-t_{10}) C_2: Frequency of use (number of days per month) following symptom assessment (t_2-t_{11})	P_1: Level of positive symptoms following cannabis use (BPRS) (t_2-t_{11}) P_2: Level of positive symptoms prior to cannabis use (t_1-t_{10})	Generalized Estimating Equation	(1) $C_1 \rightarrow P_1$* (1) $P_2 \rightarrow C_2$ (NS)	Medication adherence, other substance use	101	A: (+) B: (–) C: (+) D: (+) E: (+)
Henquet et al. (2010) / Netherlands / Established psychosis with comorbid cannabis use	t: ESM: 6 consecutive days with 12 assessments each day	C_1: Cannabis use prior symptom assessment C_2: Cannabis use following symptom assessment	P_1: Level of psychotic experience following cannabis use (ESM psychosis score) P_2: Level of psychotic experience prior cannabis use	Multilevel regression analysis	$C_1 \rightarrow P_1$* $P_2 \rightarrow C_2$ (NS)	Age, gender, alcohol use and other drug use, level of cannabis use during the week	42	A: (+) B: (–) C: (+) D: (+) E: (–)
Foti et al. (2010)/ US / First episode psychosis	t_1: Baseline t_2: 0.5 years FU t_3: 2 years FU t_4: 4 years FU t_5: 10 years FU	C_1: Change in cannabis use status (non-user – user; use > 1) (t_1-t_5) C_2: Cannabis use status prior symptom assessment C_3: Cannabis use status following symptom assessment	P_1: Changes in psychotic symptoms (SAPS) (t_1-t_5) P_2: Level of psychotic symptoms following cannabis use P_3: Level of psychotic symptoms prior cannabis use	(1) FEM (2) SEM	(1) $C_1 \rightarrow P_1$* (2) $C_2 \rightarrow P_2$* (2) $P_3 \rightarrow C_3$*	SAPS, SANS, depression; other drug use, antipsychotic medications, demographic characteristics (age, sex, and SES)	229	A: (+) B: (+) C: (+) D: (+) E: (–)

Note. BPRS = Brief Psychiatric Rating Scale; CUD = Cannabis Use Disorder; DAI = Drug attitude Inventory; DUP = Duration of untreated psychosis; ESM = Experience Sampling Method; FEM = fixed effects models; FU= Follow up; Mini = Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) ; NOS = Not otherwise specified; PAS = Premorbid Adjustment Scale, R= Range; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms ; SCL = Symptom Checklist 90 (Derogatis, 1996); SEM = Structural Equation Modeling; SES = socioeconomic status

[a] Relapse was defined as an exacerbation of psychotic symptoms that lasted for longer than 2 weeks and resulted in a change in patient management (increased observation by the clinical team; increase in antipsychotic medication or both).

[b] Quality assessment based on whether a study did (+) or did not (–): A: Control for observed confounders B: Applied Fixed Effects Analysis (Fixed effects or sibling pair analysis) C: Used temporal ordering of risk factor (lagged outcome); D: Tested for directionality; E: Explored dose-response relationships

* $p \leq 0.05$

NS $p > 0.05$

5.3 METHOD

5.3.1 SAMPLE

Patients with first episode non-organic [non-affective (ICD10 codes F20-F29) or affective (F30-F33)] psychosis (WHO, 2004), aged 18-65 were recruited from local psychiatric services in South London and assessed twice as part of research, first assessment being close to the onset of their illness. Follow-up assessment involved either a face-to-face or a telephone interview (if the individual was unable to appear in person) at least two years following the onset of their psychotic illness. Interview data was complemented by a screening of clinical records to extract healthcare use data (e.g. dates of admission/discharge, medication use). Outcome data (admission to hospital following psychosis onset) was also collected from clinical records for those who refused to take part in follow up (n=133). Comparison of outcome (risk of relapse) between those patients who agreed to take part and those who refused revealed that they were not significantly different in their risk of relapse over the two-year follow-up period following onset (χ^2 =0.30, p=0.58). This study was granted ethical approval by South London & Maudsley NHS foundation trust and Institute of Psychiatry Local Research Ethics Committee. All subjects included in the study gave written informed consent.

5.3.2 MEASURES

Diagnosis (affective vs. non-affective psychosis) was based on ICD-10 diagnosis assessed with OPCRIT (McGuffin et al., 1991). Cannabis use over the first two years following onset of psychosis was assessed using a modified version of the Cannabis Experience Questionnaire (CEQ_{mv}, cf. **Chapter 8.2.2**, Appendix II) (Di Forti, Marconi, et al., 2015). To assess the reliability of the retrospective assessment of cannabis use, I compared data on premorbid cannabis use (ever used before onset)

collected at onset of psychosis with data on premorbid cannabis use reported at follow-up. In 93% of those compared, reporting of premorbid cannabis use was consistent across both assessments (i.e., at onset and at follow-up); 4% denied premorbid use when assessed at the onset of psychosis but admitted it when re-examined at the follow up assessment, while 3% denied pre-morbid cannabis use at follow-up assessment although they had admitted use when assessed at onset. Subjects were classified based on their pattern of reported cannabis use following onset, assessing cannabis use within the first year following onset [C_{t1}] and cannabis use within the second year following onset [C_{t2}]. Two cannabis use variables were defined, including the dichotomized variable 'cannabis use status' (C_{t1}/C_{t2}) and the ordinal variable 'pattern of cannabis continuation' (CP_{t1}/CP_{t2}). The dichotomized variable 'cannabis use status' (C_{t1}/C_{t2}) classified patients during the respective time periods (t_1 & t_2) into 'not cannabis user' (NCU; no use or use only once or twice within the period under consideration) and 'cannabis user' (CU; used cannabis more than twice) categories. The ordinal variable 'pattern of cannabis continuation' (CP_{t1}/CP_{t2}, scored from 0 to 2) classified patients based on their pattern of cannabis use following onset of psychosis into (0) not cannabis user (NCU; as above), (1) intermittent cannabis user (ICU; used cannabis more than twice but not every month within the period under consideration) or (2) continued cannabis user (CCU; used cannabis every month throughout all of the follow-up months within the period under consideration). Relapse was defined as admission (yes/no) to a psychiatric inpatient unit owing to exacerbation of psychotic symptoms within the first year [R_{t1}] and the second year following the first presentation of psychosis [R_{t2}]. If the patient was hospitalized at their first presentation to psychiatric services with a diagnosis of psychosis, this was not considered as a relapse event. This definition of relapse is most commonly used in epidemiological research in psychosis (D. E. Addington, McKenzie, Norman, Wang, &

Bond, 2013; Olivares et al., 2013). Covariates included in the analyses were selected based on previous literature [including the strongest predictors for relapse in psychosis (M Alvarez-Jimenez et al., 2012)] and exploratory analysis to identify those factors that were linked to both cannabis use and relapse within the two years following onset (cf. below *Table 21.*). Taking these into consideration, I included two covariates in our analysis: (i) adherence to antipsychotic treatment plan and (ii) other drug illicit use within the first two years following onset of psychosis. Adherence to treatment plan was indexed in accordance with previous reports (L Clausen et al., 2014), whereby patients were allocated a score ranging from 1 to 3 based on information on prescription and ratings of adherence: 3=medication not prescribed or good adherence with the prescribed medication (0% - 33% of the time non-adherent) within the two years following the onset of illness; 2=medication prescribed and irregular compliance (34%-66% of the time non-compliant); 1=medication prescribed and non-compliance (67%-100% of the time non-compliant). Other drug use was defined as use of illicit drugs other than cannabis within the two years following onset. This variable was coded as an ordinal variable, ranging from 0 to 2: 0=no use; 1=experimental use (less than 6 times); 2=regular use (6 times or more)].

Table 21. Exploratory analysis (Chi-square tests) to select covariates for multiple analyses[a]

Covariates[b]	**Relapse**[b]		**Cannabis (C_t)**[b]		**Cannabis (CD_t)**[b]	
	χ^2	*p*	χ^2	*p*	χ^2	*p*
Gender	0.36	0.55	13.06	**0.0003**	13.07	**0.001**
Ethnicity	4.24	**0.04**	1.45	0.23	1.80	0.41
Age of onset	1.11	0.29	0.92	0.34	0.92	0.63
Medication adherence	15.88	**0.0004**	10.48	**0.005**	11.99	**0.02**
Premorbid cannabis use	2.13	0.14	71.36	**<0.0001**	71.57	**<0.0001**
Other illicit drug use (following onset)	8.91	**0.01**	21.92	**<0.0001**	26.33	**<0.0001**
Alcohol use (following onset)	4.26	0.12	11.10	**0.004**	13.30	**0.01**

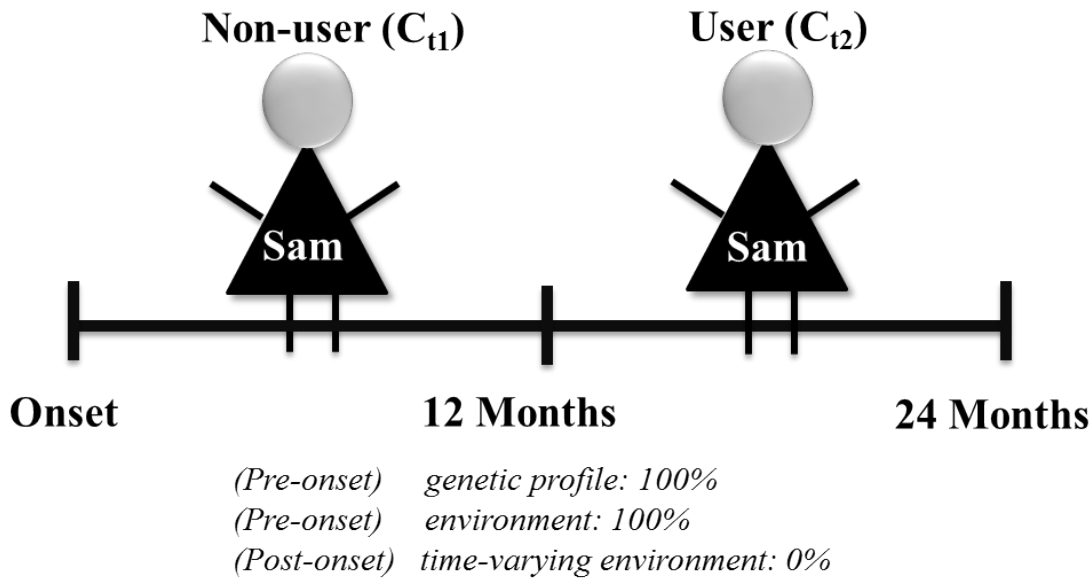
[a] Covariates were included in multiple analysis if significantly ($p \leq 0.05$) linked to relapse and cannabis use

[b]Defined as: Relapse within the two years following the onset (coded as 1: admission to a psychiatric inpatient unit owing to exacerbation of psychotic symptoms following the first presentation of psychosis, 0: no admission to a psychiatric inpatient unit following the first presentation of psychosis); Cannabis use status (C_t) within the two years following the onset of illness (coded as 0: no use or use only once or twice; 1: used cannabis more than twice); Cannabis use (CD_t) within the two years following the onset of illness (coded as 0: no use or use only once or twice, 1: used cannabis more than twice but not every month, 2: used cannabis throughout all of the follow-up months); Gender (coded as 0: Female, 1: Male); Ethnicity (coded as 0: white ethnicity, 1: non-white ethnicity), age of onset (coded as 0: referral for psychosis before age 18, 1: referral for psychosis after age 18), medication adherence within the two years following the onset of illness [coded as 1:medication prescribed and non-compliance (67%-100% of the time non-compliant), 2: medication prescribed and irregular compliance (34%-66% of the time non-compliant), 3: medication not prescribed or good adherence with the prescribed medication (0% - 33% of the time non-adherent)], premorbid cannabis use (coded as 1:Subject who had a history of regular cannabis use (defined as use at least once/month for 6 consecutive months) prior to their onset), 0: Subjects without a history of regular cannabis use prior to their onset, other illicit drug use within the two years following the onset of illness [coded as 0=no use; 1=experimental use (less than 6 times); 2=regular use (6 times or more)], Alcohol use within the two years following the onset of illness (coded as 0:<1 month daily use, 1: >1 month daily use; 2: >6 months daily use)

5.3.3 DATA ANALYSIS

In the first step, fixed-effects logistic regression models were fitted using the R package lme4 (Bates et al., 2015) for binary outcome in order to adjust for factors that vary across individuals and may affect outcome, but were not measured and do not vary over time, such as familial and genetic factors, duration of untreated psychosis or premorbid adjustment. This approach allows estimation of the effect of within-person changes over time in their pattern of cannabis use in the first year [C_{t1}/ CP_{t1}] and the second year [C_{t2}/ CP_{t2}] following onset of psychosis. This analysis estimates the likelihood of an event (e.g. here defined as relapse) during periods when an individual is exposed to the risk factor of interest (e.g. cannabis use) compared to when the same individual is not exposed to the risk factor (cf. exemplified in *Figure 16.*). Hence, each subject becomes their own control in fixed-effects models, wherein only subjects with a change in exposure (C_{t1}.C_{t2}/CP_{t1}.CP_{t2}) over the specified time-period are selected. As a result, if one subject is more likely to relapse during a period in which the subject was exposed to cannabis than during a period in which the subject was unexposed, this would indicate an effect of cannabis that is independent of the unmeasured potential confounding factors that did not change over this time period, such as the genetic make-up of the person, personality, age, gender and life events prior to the onset. Factors that vary over time following onset (e.g. other drug use, medication adherence) are adjusted for, as done in conventional multiple regression analysis. Other illicit drug use and medication adherence were included as covariates that change over time in the multiple models.

Figure 16. Adaptation of sibling-design for fixed-effects analysis to assess change in cannabis use (C_t) over time



In the second step, cross-lagged autoregressive path models were estimated using the lavaan package (Rosseel, Oberski, & Byrnes, 2011) to investigate the directionality of association. Relapse variables (R_{t1}-R_{t2}) were treated as dependent variables with cannabis use (C_{t1}- C_{t2}/CP_{t1}- CP_{t2}) variables as the independent variables to examine whether cannabis use predicted subsequent risk of relapse and vice versa for the reverse lagged association to examine whether relapse (R_{t1}-R_{t2}) predicted cannabis use (C_{t1}- C_{t2}/CP_{t1}- CP_{t2}). Model paths were estimated while controlling for other illicit drug use and medication adherence. The models were fitted using the robust weighted least squares (WSL) approach. In the first step, I fitted a saturated path model in which all possible paths to the endogenous variables (C_{t2} and R_{t2}) were specified. In the second step, a more parsimonious model was tested that included only the statistically significant ($p \leq 0.05$) pathways tested. Model goodness of fit was assessed on the basis of a number of fit indices, including the model chi-squared goodness of fit statistic (non-significant or small chi-square value indicating that the model fitted the data well),

the root mean-squared error of approximation (RMSEA, with values of 0.05 indicating good fit and values up to 0.08 representing reasonable errors of approximation) (MacCallum, Browne, & Sugawara, 1996) and the comparative fit index (with values of 0.95 being acceptable and higher than 0.95 indicating good fit) (Hu & Bentler, 1999).

5.4 RESULTS

5.4.1 SAMPLE CHARACTERISTICS

Two hundred and twenty patients with a first episode of psychosis were included in the analysis, comprising 213 (96.8%) subjects that were interviewed face-to-face and 7 (3.2%) that were interviewed in a phone conversation. Within the first two years following onset of illness, 35.5% of patients experienced a relapse in the form of admission to psychiatric hospital. Out of 121 subjects with pre and/or post onset regular cannabis use, only 3 (3.7%) subjects started using cannabis (use $\geq$ 2 times) following onset of psychosis (with no previous history of regular use). Sixty-nine (57 %) had used cannabis regularly prior to the onset and used it subsequently either intermittently or continuously, and 52 (43%) had a history of regular use prior to the onset of psychosis but did not use it regularly following onset. Fifty-nine (26.8%) patients had never tried cannabis in their lifetime. On comparing the different groups based on their cannabis use patterns (*Table 22.*), it appeared that they significantly differed in the age of onset of their psychosis (Kruskal-Wallis, p=0.02) and with regard to gender (χ^2=13.07, p=0.001). No differences between the groups were found for diagnosis (affective vs. non-affective psychosis) (χ^2=4.18, p=0.12). With regard to outcome, the different cannabis use groups (NCU vs. ICU vs. CCU in the two years following the onset) were significantly different with regard to risk of relapse (χ^2=13.96, p=0.0009). To illustrate, the highest risk of relapse was present in those who used it continuously following the onset while those who did not continue cannabis use were at lowest risk (59.1% vs. 28.5%). Furthermore, the cannabis use groups significantly differed with regard to the level of medication adherence (χ^2=11.99, p=0.02), e.g. those who continued to use cannabis were less likely to have remained adherent to their antipsychotic treatment. Similarly, the degree of other illicit drug use (other than cannabis) was different between the

cannabis use groups (χ^2=26.33, p<0.0001), which indicated that those who continued to use cannabis also used other illicit drugs more frequently throughout the two years following onset of psychosis.

Table 22. Demographic information

Onset characteristics	All subjects	Non-use (NCU)	Intermittent user (ICU)	Continued user (CCU)	*p*
Number of subjects	220 (100%)	151 (68.6%)	25 (11.4%)	44 (20%)	
Age of onset (M/SD)	28.62 (8.58)	29.52 (8.92)	28.79 (8.94)	25.44 (6.32)	**0.02**
Gender (n male)	130 (59.1%)	77 (51%)	19 (76%)	34 (77.3%)	**0.001**
Ethnicity (n non-white)	147 (66.8%)	97 (64.2%)	17 (68%)	33 (75%)	0.41
Onset diagnosis (n non-affective)	184 (83.6%)	126 (83.4%)	18 (72%)	40 (90.9%)	0.12
Pre-onset (regular) cannabis use (n yes)	118 (53.6%)	52 (34.4%)	23 (92%)	43 (97.7%)	**<0.0001**
Course characteristics	**All subjects**	**Non-use (NCU)**	**Intermittent user (ICU)**	**Continued user (CCU)**	***p***
Other illicit drug use					**<0.0001**
No use n	186 (84.5%)	139 (92%)	19 (76%)	28 (63.6%)	
Experimental use n	13 (5.9%)	6 (4%)	3 (12%)	4 (9.1%)	
Regular use n	21 (9.5%)	6 (4%)	3 (12%)	12 (27.3%)	
Medication adherence					**0.02**
Non-adherence n	39 (17.7%)	24 (15.9%)	6 (24%)	9 (20.5%)	
Irregular-adherence n	92 (41.8%)	55 (36.4%)	11 (44%)	26 (59.1%)	
Full-adherence n	89 (40.5%)	72 (47.7%)	8 (32%)	9 (20.5%)	
Relapse (yes) in 2 years following onset	78 (35.5%)	43 (28.5%)	9 (36%)	26 (59.1%)	**0.0009**

Note. M=Mean; n=number of subjects; SD=Standard Deviation.

[a] *p*-value estimates from Kruskal-Wallis test for means and Chi-square tests for independence for percentages to compare all cannabis groups

5.4.2 Fixed-effects analysis: Changes in cannabis use and relapse

As shown in *Table 23.*, the unadjusted fixed-effects analysis showed that risk of relapse was higher during the year in which cannabis was used (more than twice) 1.18[95% CI 1.08-1.29] when compared to the year in which cannabis was not used, and this effect remained significant when controlling for time-varying factors such as medication adherence and other illicit drug use 1.13[95% CI 1.03-1.24]. Furthermore, there was a dose-response relationship between pattern of cannabis continuation and risk of relapse, such that one unit change in cannabis use pattern signifying greater regularity in cannabis use over time [e.g. from intermittent cannabis use (CP_{t1}) to continued cannabis use (CP_{t2})] was associated with an increase in odds for risk of relapse of 1.10[95% CI 1.05-1.15]. This effect was reduced but remained significant when controlled for medication adherence and other illicit drug use (1.07[95% CI 1.02-1.13]). In this model, medication non-adherence (0.92[95%CI 0.87-0.97]) but not other illicit drug use (1.04[95% CI 0.98-1.12]) remained a significant predictor for risk of relapse.

Table 23. Fixed-effects logistic regression analysis: Risk of relapse

	OR	95% CI
Change in 'cannabis use status' (C_t)		
Simple Analysis		
Cannabis use status ($C_{t1} – C_{t2}$)	1.18	1.08 – 1.29
Multiple Analysis		
Cannabis use status ($C_{t1} – C_{t2}$)	1.13	1.03 – 1.24
Medication adherence*	0.92	0.87 – 0.97
Other illicit drug use*	1.05	0.98 – 1.12
Change in 'pattern of cannabis continuation' (CP_t)		
Simple Analysis		
Pattern of cannabis continuity ($CP_{t1} – CP_{t2}$)	1.10	1.05 – 1.15
Multiple Analysis		
Pattern of cannabis continuity ($CP_{t1} – CP_{t2}$)	1.07	1.02 – 1.13
Medication adherence*	0.92	0.87 – 0.97
Other illicit drug use*	1.04	0.98 – 1.12

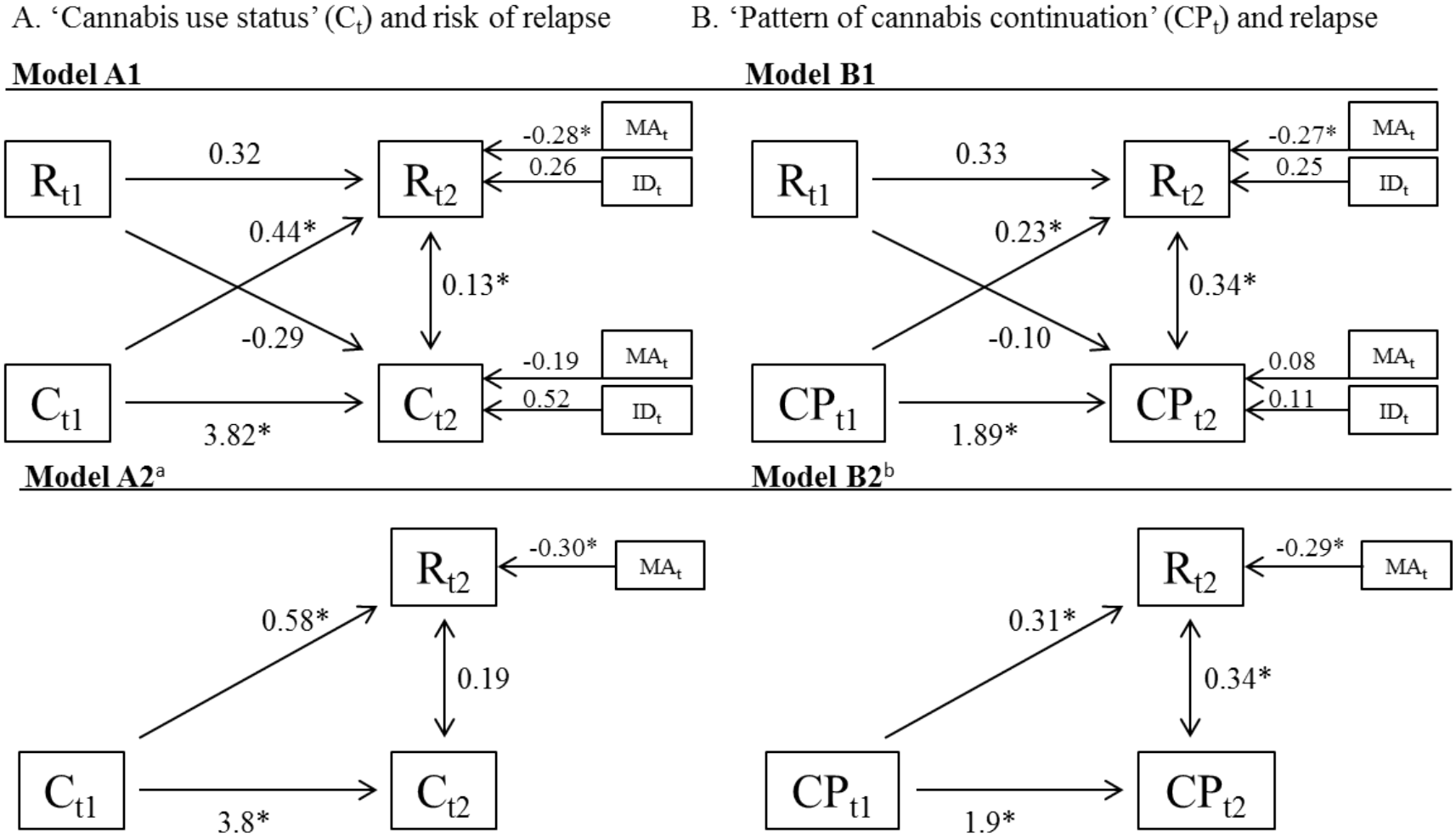
Note. Change (increase) in 'cannabis use status' (C_t) = change from 'not cannabis user' to 'cannabis user'; Change (increase) in 'pattern of cannabis continuation' (CP_t) = change in one unit [(0) not cannabis user; (1) intermittent cannabis user; (2) continued cannabis user]
*Included as random effects

5.4.3 Cross-lagged modelling: Continuation of cannabis use and subsequent relapse

Examining the different pathways in the saturated cross-lagged path model (cf. Model A1 and Model B1, *Figure 17.*) revealed that the effect of cannabis use (during the first year of follow-up; t_1) on subsequent (during the second year of follow-up; t_2) risk of relapse was significant for 'cannabis use status' ($C_{t1} \rightarrow R_{t2}$:$\beta$ =0.44, p=0.04), as well as 'pattern of cannabis continuation' ($CP_{t1} \rightarrow R_{t2}$:$\beta$ =0.23, p=0.05), while controlling for medication adherence and other illicit drug use. The alternative paths, i.e. relapse within the first year (t_1) following onset of psychosis predicting subsequent (t_2) 'cannabis use status' ($R_{t1} \rightarrow C_{t2}$:$\beta$ =-0.29, p=0.59) and 'pattern of cannabis continuation' ($R_{t1} \rightarrow CP_{t2}$: β =-0.10, p=0.76) were not significant, indicating a uni-directional effect of cannabis use on risk of relapse of psychosis. Of the autoregressive pathways tested in

those models, presence of cannabis use at t_1 predicted presence of cannabis use at t_2 ($C_{t1} \rightarrow C_{t2}$:$\beta$ =3.82, $p \leq 0.001$) and pattern of cannabis continuation at t_1 was a significant predictor for pattern of cannabis continuation at t_2 ($CP_{t1} \rightarrow CP_{t2}$:$\beta$ =1.8, $p \leq 0.001$), while relapse at t_1 was not significantly associated with relapse at t_2 (Model A1: $R_{t1} \rightarrow R_{t2}$:$\beta$ =0.32, p=0.18; Model B1: $R_{t1} \rightarrow R_{t2}$:$\beta$ =0.33, p=0.17). Consistent with the results from the fixed-effects model, only medication adherence (MA) (Model A1: $MA_t \rightarrow R_{t2}$:β =-0.28, p=0.04; Model B1: $MA_t \rightarrow R_{t2}$:β =-0.27, p=0.05) but not other illicit drug use (ID) (Model A1: $ID_t \rightarrow R_{t2}$:β =0.26, p=0.10; Model B1:$ID_t \rightarrow R_{t2}$:β =0.25, p=0.11) was significantly linked to risk of relapse. Cannabis use at t_2 was not predicted by other illicit drug use (Model A1: $ID_t \rightarrow C_{t2}$:β =0.52, p=0.70; Model B1: $ID_t \rightarrow CP_{t2}$:β =0.11, p=0.66) or medication adherence (Model A1: $MA_t \rightarrow C_{t2}$:β = -0.19, p=0.58; Model B1: $MA_t \rightarrow CP_{t2}$:β =0.12, p=0.53). Model 2, in which all non-significant paths from Model 1were dropped yielded a good fit to the data (Model A2: CFI=1.00, RMSEA$\leq$0.001, Model B2: CFI=1.00, RMSEA$\leq$0.001). The strengths of associations are presented for cannabis use predicting subsequent relapse (Model A2: $C_{t1} \rightarrow R_{t2}$: β = 0.58, p=0.004; Model B2: $CP_{t1} \rightarrow R_{t2}$: β = 0.31, p=0.004), cannabis use predicting subsequent cannabis use (Model A2: $C_{t1} \rightarrow R_{t2}$: β = 3.8, p<0.001; Model B2: $CP_{t1} \rightarrow CP_{t2}$: β = 1.9, $p \leq 0.001$) and medication non-adherence predicting relapse (Model A2: $MA_{t1} \rightarrow R_{t2}$: β = -0.30, p=0.02; Model B2: $MA_t \rightarrow R_{t2}$: β = -0.29, p=0.03).

Figure 17. Cross-lagged path analysis



Note. C_t = 'Cannabis use status' (non-user – user) in the first year (C_{t1}) and in the second year (C_{t2}) following the onset; CP_t = 'Pattern of cannabis continuation' (non-user – intermittent user – continued user) in the first year (CP_{t1}) and in the second year (CP_{t2}) following the onset; ID_t: Illicit drug use (score 0-2) within the two years following the onset; MA_t: Medication adherence (score 0-2) within two years following the onset; R_t = Relapse (yes – no) in the first year (R_1) and in the second year (R_2) following the onset.

[a] Goodness of fit indices: $\chi 2$ (1) = 0.33, p=0.565; RMSEA = 0.00, p=0.659; CFI = 1.00.

[b] Goodness of fit indices: $\chi 2$ (1) = 0.24, p=0.625; RMSEA = 0.00, p=0.708; CFI = 1.00.

* $p < 0.05$

5.5 Discussion

In this study, I estimated the longitudinal effects of cannabis use status and pattern of continued cannabis use following the onset of psychosis on risk of relapse. The results implicate both change in cannabis use status (e.g. from user to non-user) as well as change in pattern of continued cannabis use within the first two years following onset as a risk factors for relapse. By virtue of the study design employed here, I was able to compare periods of use with periods of non-use within the same individual, signifying that this association cannot be explained by stable premorbid confounding factors such as shared familial and genetic vulnerability, predisposing personality traits, duration of untreated psychosis, childhood trauma, expressed emotion or cannabis use history prior to the onset of psychosis. Furthermore, changes in cannabis use status and pattern of cannabis continuation over time were linked to relapse independent of the effects of other potential confounders that vary over time such as medication adherence and other illicit drug use. These results indicate that the association found here is unlikely to result from a common underlying vulnerability shared by cannabis use and psychotic relapse, such as a genetic predisposition for psychosis that is also linked to cannabis use (R. A. Power et al., 2014). This is consistent with a study that failed to replicate the association between polygenic risk for psychosis and cannabis use (Di Forti, Vassos, et al., 2015), indicating that even if a shared genetic vulnerability exists, this contribution would not fully account for the adverse effects of cannabis use on outcome in those patients with psychosis who continue using the substance. In line with this, another study (Sherva et al., 2016a) that compared genome wide association (GWAS) data concerning cannabis use with GWAS data on 5 different psychiatric disorders found a very small overlap with depression but none with schizophrenia. Overall, this line of evidence and my results are in accordance with previous research

employing fixed-effects analysis which reported that change in cannabis use status (from non-user to user) was linked to change in psychotic symptom severity (Foti et al., 2010). My findings also support a dose-response relationship, i.e. the longer the period of continued (monthly) cannabis use following onset of psychosis, the more likely a patient is to experience a relapse, consistent with previous evidence (J. McGrath et al., 2010) that duration of exposure since first use of cannabis was significantly linked to psychotic outcome in previously healthy individuals. My results from cross-lagged path analysis also indicate that cannabis use status/ pattern of continued cannabis use following onset of psychosis is predictive of subsequent relapse but not vice versa, suggesting that continuation of cannabis use following onset of psychosis is a direct risk-modifier for relapse in psychosis. These results are consistent with previous studies in patients with pre-existing psychosis that reported cannabis use as a predictor for an increase in severity of psychotic symptoms in both the short-term (1 week) (Henquet et al., 2010) and longer-term (10 months) (Degenhardt et al., 2007) and suggest that the association between cannabis use and relapse of psychosis is unlikely to be the consequence of self-medication (Dixon, Haas, Weiden, Sweeney, & Frances, 1991).

Some limitations need to be considered when interpreting my results. While clinical data was assessed prospectively using patients' clinical records, cannabis use pattern following the onset of illness relied on retrospective self-reported assessments without objective drug screens. However, cannabis use information obtained at research interview was further validated by screening patient records as well as reports of premorbid cannabis use (ever used) that was collected at the baseline research assessment at onset, revealing a very high concordance (93%) between self-report data of cannabis use at the two research assessment points (onset and follow-up). Underreporting of cannabis use has also been found to be less of an issue in research

studies, when self-report data on cannabis use has been compared to objective measures such as urine drug screen (Di Forti et al., 2014). It is also important to note that the main predictor variable (pattern of cannabis continuation following onset) did not capture cumulative exposure to cannabis per year of follow up, since this was not feasible to assess with the retrospective cannabis assessment I employed in this study. Furthermore, although the statistical methods applied in this study were designed to minimize the possibility of a non-causal explanation for the association between continued cannabis use and relapse, it is possible that other unmeasured factors changing over time may have influenced the relationship. Nevertheless, I controlled for the most significant previously identified time-variant risk factors that have been linked to psychosis relapse (M Alvarez-Jimenez et al., 2012). Hence, it seems unlikely that this was the case. Notwithstanding these limitations, results presented here have important implications. Together, these results suggest that it is more likely than not that continued cannabis use following onset of psychosis is causally associated with increased risk of relapse of psychosis resulting in psychiatric hospitalisation. As cannabis use is a potentially modifiable risk factor that has an adverse influence on the risk of relapse of psychosis and hospitalisation in a given individual, with limited efficacy of existing interventions (Wilson & Bhattacharyya, 2016), these results underscore the importance of developing novel intervention strategies and demand urgent attention from both clinicians and health policy makers. Results from both of the analytical methods employed (fixed-effects and cross-lagged path analysis) were consistent and point towards a dose-response relationship between continued cannabis use and relapse of psychosis resulting in hospitalisation. They implicate cannabis use as a risk-modifying factor, suggesting that discontinuation of cannabis use following the onset of psychosis may help in reducing the risk of relapse.

6 GENERAL DISCUSSION

The prevalence rates of young people using cannabis as risen in recent years, as well as the potency of cannabis (M. A. ElSohly et al., 2016; Hasin et al., 2015). This has added fuel to debate around cannabis legislation and its medical or recreational use, especially in light of the high rates of cannabis use that are reported in those presenting with their first episode. Of particular concern is that this group of users has been found to be more vulnerable to the psychotomimetic effects of THC (D'Souza et al., 2005; Henquet et al., 2010) and that those individuals often comprise high rates of users that continue using the substance following the onset of the illness. Given the ongoing debate regarding its link with psychosis (Robin M. Murray & Di Forti, 2016), and the reliance on cross-sectional uncontrolled investigations looking at outcome such as relapse and symptom exacerbation (Schoeler, Monk, et al., 2016; Zammit et al., 2008a), it is critical from a translational research point of view to better understand whether cannabis use may play a causal role within the course of illness following a first episode psychosis – in particular since "*cannabis represents the most potentially modifiable risk factor for psychosis*" [(Suzanne H. Gage, Hickman, & Zammit, 2016), Page 549, Paragraph 2]. However, studies evaluating multifactorial risk models for relapse in patients with psychosis often left out cannabis use in their considerations (D. Addington et al., 2010; M. Alvarez-Jimenez et al., 2012; Austin et al., 2015; Gearing et al., 2009; Hui et al., 2013; D. Robinson et al., 1999; Sipos, Harrison, Gunnell, Amin, & Singh, 2001; Üçok et al., 2006). In my thesis, I therefore used a combination of methods in order to minimize the effect of potential confounding factors when establishing causality, resulting in the following main findings:

(1) **Paper 1** (Schoeler, Monk, et al., 2016): Investigation of the unadjusted effects of continued and discontinued cannabis use following the onset and risk of

relapse in patients with FEP and established psychosis (meta-analysis): Data was pooled together from 24 studies (16 565 participants) to compare the groups (1) continued cannabis user, (2) discontinued cannabis user and (3) non-user in their relapse outcome. Independent from the stage of illness, continued cannabis users had more numerous relapses, longer hospitalisations and more severe positive symptoms when compared to non-users. These adverse effects were not present in patients who discontinued following the onset. The findings implicate that reductions in cannabis use may improve outcome in patients with psychosis, although causality cannot be established due to the correlational nature of the association.

(2) **Paper 2** (Schoeler, Petros, Di Forti, Klamerus, et al., 2016): Investigation of the adjusted effects of continuation, frequency and type of cannabis use on relapse in the first two years following onset of psychosis (follow-up study): 256 FEP patients presenting to psychiatric services in South London were prospectively recruited and followed up in order to estimate the effect of different patterns of cannabis use based on (a) continuity of use following onset of psychosis, (b) potency of cannabis consumed and (c) frequency of use following onset of their illness, while taking into consideration important confounding factors. The results showed that former regular users who stopped after onset had the most favourable illness course with regard to relapse. Those who continued high-frequency users (daily use in all 24 months) of high-potency cannabis ("skunk-like") had the worst outcome, indexed as an increased risk for a subsequent relapse, more numerous relapses, fewer months until a relapse occurred and more intense psychiatric care following onset of psychosis. The results indicate that the adverse effects of continued use of cannabis following the onset of FEP

depend on the specific patterns of use, even when controlled for confounders such as medication non-adherence, other substance use and other onset demographic and clinical measures. Interventions may focus on persuading cannabis-using patients with psychosis to reduce use or shift to less potent forms of cannabis.

(3) **Paper 3** (Schoeler, Petros, Di Forti, Pingault, et al., 2016): Investigation of the temporal relationships between continued cannabis use and risk of relapse in the first two years following onset of psychosis using a quasi-experimental design: Longitudinal modelling was employed (fixed-effects analysis, cross-lagged path analysis) to examine whether the association between changes in cannabis use and risk of relapse over time is the result of non-causal explanations, including shared-vulnerability between psychosis and cannabis use, confounding effects of other illicit drug or medication non-adherence, reverse causation (psychosis increasing the risk of cannabis use) or indeed a causal effect of cannabis use on psychosis relapse. Within-subject comparisons (thereby controlling for time-invariant unobserved confounders such as genetic/premorbid environment) revealed that there was an increased risk of experiencing a relapse of psychosis in periods of cannabis use relative to periods of no use. The effect was also present for change in pattern of continuation of cannabis use, suggesting a dose-dependent relationship. The exploration of directionality confirmed that this association reflected an effect of cannabis use on subsequent risk of relapse, rather than an effect of relapse on subsequent cannabis use. The results demonstrate a dose-dependent association between change in cannabis use and relapse of psychosis, that is unlikely to be a result of self-medication or genetic and environmental confounding.

6.1 FINDINGS

Overall, my results implicate that cannabis is likely to represent a causal risk factor for relapse in first episode psychosis – an effect that (a) is likely to be of a magnitude that is clinically relevant, (b) likely to exerts its effects in the form of a dose-response relationship, (c) unlikely to be explained by other sources of confounding, (d) unlikely to be the result of self-medication (reverse causation) and (e) reflects one risk factor among numerous others (i.e. cannabis constitute a component cause of psychotic relapse rather than a sufficient cause). Several findings in my thesis provide evidence for this conclusion, i.e. speak for causality. Those are illuminated in the following paragraphs, using the structure suggested by the Hill-criteria (A. B. Hill, 1965):

1. *Strength: Is the magnitude of association between continued cannabis use and risk of relapse strong enough to raise clinical concerns?*

The results from my meta-analysis [**Paper 1,** (Schoeler, Monk, et al., 2016)] indicate that cannabis users are significantly at higher risk for relapse when compared to non-users or those who discontinued following the onset. When looking at a more detailed definition of cannabis use in **Paper 2** (Schoeler, Petros, Di Forti, Klamerus, et al., 2016), I found that heavy use of high-potency cannabis was one of the strongest predictors for relapse (OR = 3.28). Among the other predictors included in this model, significant increases in risk for relapse were only present for medication non-adherence (OR = 3.25), non-white ethnicity (OR = 2.36) and increased onset severity (indexed as care intensity at onset, OR = 1.37). While early studies proposed that medication adherence was the most crucial factor with regard to relapse-prevention (D. Robinson et al., 1999), my findings suggest that the strength of effect of cannabis is most likely to be of at least equal significance. To illustrate, the adjusted risk estimates found in my

analysis indicated a 1.9 higher risk for relapse in continued skunk users (taken from propensity score matched analysis, with RR = 1.9, 57% vs. 30%). When putting the magnitude of effect into context, this estimate is similar the adjusted effects of antipsychotic treatment (placebo group vs. medicated group), in which a 2.4 times higher risk (64% vs. 27%) for relapse was found for those not being treated with medication (Stefan Leucht et al., 2012). The estimate is also comparable to that found for the effect of psychotherapy (TAU vs. CBT), in which a 1.9 times higher risk (34% vs. 18%) was present in those not receiving psychotherapy (Gumley et al., 2003).

These results therefore suggest that reductions in cannabis use may lead to clinically meaningful improvement in outcome that is comparable in its efficacy to those interventions recommended by the NICE (National Institute for Health and Care Excellence) guidelines for early intervention in psychosis, including antipsychotic drug treatment in conjunction with psychological interventions (NICE). Furthermore, although antipsychotic treatment is an effective intervention reducing the risk of relapse (Stefan Leucht et al., 2012), its preventative effects often remain unrealized in those not adhering to the treatment plan, which is often related to side-effects such as weight gain and metabolic syndrome (Patel et al., 2009). Hence, especially in those unwilling to take their medication, a reduction in cannabis use would be crucial in order to reduce risk of relapse.

2. Consistency: Is the effect consistent across different measures of relapse?

In the meta-analysis (**Paper 1**), I found that continued cannabis use was related to an increased risk of relapse, longer times spent in hospital and more severe positive symptoms, which speaks for its consistency across measures that capture positive psychotic symptomatology. Although this analysis did not control for important

confounders, the results are in accordance with those from the adjusted prediction models (**Paper 2**), in which the effect of continued high-frequency use (daily use in all 24 months) of high-potency cannabis ("skunk-like") was linked to risk of a subsequent relapse, more numerous relapses, fewer months until a relapse occurred and a higher care intensity index (i.e. a higher risk that the relapse event involved admission under section) in the two years following onset of illness. Hence, these findings are in accordance with Hill's (A. B. Hill, 1965) criteria of consistency, as well as with other longitudinal studies that reported a link between continued use of cannabis and risk of relapse (Bergé et al., 2016; B. Schimmelmann et al., 2012), duration of stay in hospital (Leeson et al., 2012), time until a relapse occurred (Linszen et al., 1994), and positive symptoms severity (Baeza et al., 2009; L. Clausen et al., 2014; Foti et al., 2010; Harrow et al., 2005; Hinton et al., 2007; Seddon et al., 2015).

3. *Specificity: Does continued cannabis use has a specific relationship with psychotic relapse?*

When elaborating the issue of specificity of the effects of continued cannabis use, it should be evaluated (a) whether the effect of cannabis is linked solely (i.e. specifically) to measures of psychotic symptom exacerbation or, alternatively, whether it is also linked to a range of other clinical (non-psychotic) and functional outcomes (i.e. non-specific with regard to outcome). Second, it should be elaborated (b) whether the effect found for cannabis is also present for other (psychoactive) substances such as cigarettes and other illicit drugs. With regard to question (a), the results from the meta-analysis (**Paper 1**) indicated that cannabis was linked to all measures assessing psychotic symptoms (relapse, time spent in hospital, positive symptom severity), while there was no clear effect on negative symptoms or level of functioning, indicating some level of

specificity with regard to outcome. Similarly, in my other meta-analysis (Schoeler, Kambeitz, et al., 2016), no aversive effects of cannabis use in patients with psychosis were present for memory function, level of functioning or severity of depression. Unfortunately, the results from my follow up study (**Paper 2** and **Paper 3**) do not allow to draw conclusions regarding the specificity of effects with regard to outcome, since I focused exclusively on exacerbation of positive symptoms (i.e. risk of psychotic relapse, time until a relapse occurred, length of hospital stay, care intensity at follow up). When looking at the available literature, the evidence from follow up studies is rather mixed. For instance, continued cannabis use significantly predicted poor outcome for a range of outcomes assessed at follow up, including risk of relapse (Bergé et al., 2016; B. Schimmelmann et al., 2012), length of time spent in hospital (Leeson et al., 2012), positive symptoms severity (Baeza et al., 2009; L. Clausen et al., 2014; Foti et al., 2010; Harrow et al., 2005; Hinton et al., 2007; Seddon et al., 2015), risk of non-remission (B. Schimmelmann et al., 2012), risk of continuous illness course (Grech et al., 2005a), illness severity (B. Schimmelmann et al., 2012), functioning (L. Clausen et al., 2014; Gonzalez-Blanch et al., 2015; B. Schimmelmann et al., 2012; Seddon et al., 2015), negative symptoms severity (Seddon et al., 2015), depressive symptoms (Seddon et al., 2015; J. Stone et al., 2014) and quality of life (Pencer et al., 2005). To the contrary, other follow up studies did not find a link between continued cannabis use and risk of relapse (Caseiro et al., 2012; Faber et al., 2012; Faridi et al., 2012), positive symptoms severity (Faber et al., 2012; Faridi et al., 2012; González-Pinto et al., 2011; Rais et al., 2010; Stirling et al., 2005), time spent in hospital/time spent in relapse (L. Clausen et al., 2014; Faber et al., 2012; Rais et al., 2008), symptomatic remission (Colizzi et al., 2015; Faber et al., 2012; Faridi et al., 2012), risk of continuous illness course (Sorbara et al., 2003), functional remission (Faber et al., 2012), level of

functioning (Baeza et al., 2009; Bergé et al., 2016; Faber et al., 2012; González-Pinto et al., 2011; Hinton et al., 2007; Stirling et al., 2005), clinical recovery (Faber et al., 2012), employment status (Pencer et al., 2005; Sorbara et al., 2003), negative symptom severity (Baeza et al., 2009; L. Clausen et al., 2014; Faridi et al., 2012; González-Pinto et al., 2011; Grech et al., 2005a; Hinton et al., 2007; Rais et al., 2010; J. Stone et al., 2014), disorganized symptoms (L. Clausen et al., 2014) and depressive symptoms (Baeza et al., 2009; Foti et al., 2010; Hinton et al., 2007). Nevertheless, overall it seems that a greater body of evidence is in support of the link between cannabis use and psychotic symptoms, while findings regarding functioning and affective symptoms are less consistent. Furthermore, evidence is more clear when a more valid methodological approach was employed, i.e. by assessing changes is symptoms over time. For instance, continued cannabis use predicted worsening of psychotic symptoms (Degenhardt et al., 2007; Foti et al., 2010; Henquet et al., 2010), and discontinued cannabis use was associated with fewer improvements in functioning (González-Pinto et al., 2011; J. Stone et al., 2014). Adverse effects with regard to other clinical measures are less obvious, e.g. no effect of changes in cannabis patterns on changes in depressive symptoms was found in FEP patients (Foti et al., 2010; Hinton et al., 2007) and patients with established psychosis (Degenhardt et al., 2007), and there were no differences in changes in symptoms between continuer and discontinuer were for negative symptoms (González-Pinto et al., 2011; Hinton et al., 2007). This is in line with experimental evidence of the acute effects, which clearly supports a link with psychotic symptoms (Barkus et al., 2011; Sagnik Bhattacharyya, Atakan, et al., 2015b; D'Souza et al., 2008; Englund et al., 2015; P. Morrison et al., 2009; Radhakrishnan, Skosnik, et al., 2015; Tunbridge et al., 2015; Van Wel et al., 2015), while the acute administration of THC did not result in changes in depressive symptoms (Englund et al., 2015; Wachtel et al.,

2002) or mood (Marieke Liem-Moolenaar et al., 2010). Nevertheless, in order to arrive at a more robust conclusion, future follow up studies looking at changes in cannabis use and outcome other than psychotic symptoms are warranted.

Regarding question (b), I controlled for the effects of cigarette and alcohol use, as well as for other illicit drug use in my prediction models (**Paper 2**). When predicting risk of relapse, none of those predictors independently predicted relapse beyond the effects of cannabis, although there was an effect of cigarette use and illicit drug use following onset of psychosis on the number of relapses (IRR=1.73, p=0.01 and IRR=1.79, p=0.03). Results from observational evidence are rather inconclusive in this context; For instance, a 3-year follow up of FEP patients reported that cigarette use following the onset was significantly linked to relapse (HR = 1.4) when controlled for medication non-compliance (Hui et al., 2013), which is also supported by one study in FEP patients that found a link between cigarette use and number of readmissions following the onset (Kobayashi et al., 2010). However, both studies did not consider cannabis use and other illicit drug use in their prediction models (Hui et al., 2013; Kobayashi et al., 2010) and other studies failed to find a link between cigarette use and relapse/level of positive symptomatology when controlled for alcohol and other illicit drug use in patients with established psychosis (Cooper et al., 2012). Regarding other illicit drug use, several studies that have investigated the effects of substance use in general are in accordance with my findings and have reported that ongoing substance use significantly predicted risk of relapse (Levy et al., 2012; A Malla et al., 2008; Turkington et al., 2009; D Wade et al., 2006). Problematically, no distinction between the different substances that were used was made and, in fact, cannabis use remained the most commonly used drug of abuse in those studies (Levy et al., 2012; D Wade et al., 2006) or the most commonly used drug following alcohol use (A Malla et al., 2008;

Turkington et al., 2009), for which reason conclusions regarding the independent effects of illicit drug use other than cannabis are limited. Nevertheless, when distinguishing between the different drugs of abuse, D Wade et al. (2006) reported an increased risk for inpatient admission following the onset for those with CUD, those with SUD (other than cannabis or alcohol), but not those with alcohol use disorder (AUD). In line with this, it was reported that amphetamine use after a period of abstinence in patients with chronic psychosis increased the risk of the emergence of a subsequent relapse (Sato, Chen, Akiyama, & Otsuki, 1983). Similarly, it has been reported that amphetamine can induce psychotic symptoms in healthy subjects (C. Curran, Byrappa, & Mcbride, 2004) and exacerbate symptoms in those with a pre-existing psychotic disorder (Abi-Dargham, 2004), implicating that ongoing stimulant use may increase the risk for re-emergence of psychotic symptoms in FEP patients. Nevertheless, my results suggest that the adverse effects of cannabis use were independent from the effects cigarette use and other illicit drug use each other, pointing to the possibility that cannabis perhaps exerts its effects via different neural pathways. For instance, while psychostimulants such as cocaine, amphetamines and nicotine increase cortical and subcortical dopamine levels (Berke & Hyman, 2000; Centonze et al., 2004; Drevets et al., 2001; Yoder et al., 2007), THC does not act on dopamine release directly but via the CB_1-driven modulation of glutamate and GABA neurons in the nucleus accumbens and ventral tegmental area [(Kuepper et al., 2010), cf. *Figure 6.*, **Chapter 2.2**]. To illustrate, whereas haloperidol (DA D_2) receptor antagonist reversed the amphetamine-induced psychotic symptoms in healthy human subjects (Angrist, Lee, & Gershon, 1974) and patients with a pre-existing psychotic disorder (Sato et al., 1983), no such preventative effects of haloperidol were present for THC-induced psychotic symptoms in healthy subjects (D'Souza et al., 2008). Consistent with this, while THC administration led to a

small decrease in the binding of a dopamine tracer (3%) in the striatum (Bossong et al., 2009), larger effects were reported for other stimulant drugs such as nicotine (8%-37%) (Brody et al., 2009; Brody et al., 2004), alcohol (15%) (Boileau et al., 2003), amphetamine (12%-16%) in the striatum (Drevets et al., 2001; Martinez et al., 2007; Oswald et al., 2005), or cocaine (12%) (Schlaepfer, Pearlson, Wong, Marenco, & Dannals, 1997) in the striatum – this may further implicate that the psychotomimetic effects of THC are only partially mediated by striatal dopamine release. My results also indicate that ongoing alcohol use following onset is not a predictor for relapse. This is consistent with other studies in FEP patients that reported no effect of alcohol use on risk of relapse (D Wade et al., 2006), as well as population based studies that did not find a link between alcohol use and onset of psychosis (Di Forti, Marconi, et al., 2015; David M Fergusson et al., 2005; Henquet et al., 2004; Zammit et al., 2002). In accordance, another study in cocaine-dependent users found that cannabis use but not alcohol use predicted cocaine-induced psychosis (CIP) (Trape et al., 2014).

Overall, the results are in favour of rather specific effects of cannabis on relapse and psychotic symptomatology, i.e. are not supportive of the hypothesis stated by the shared-vulnerability model, which proposed that individuals who develop (any/non-specific) mental illness are also more likely to use (any/non-specific) substance as a results of a common genetic contribution (Ksir & Hart, 2016a). Instead, my results indicate that cannabis exerts its adverse effects on psychotic symptoms exacerbation independent from the use of other substances. However, this does not rule out the possibility of interactive effects between cannabis use and other drug use in predicting psychotic symptoms (McKetin et al., 2013), which I have not investigated further in my thesis.

4. *Temporality: Does cannabis use precede the relapse event or is it a subsequent event following the relapse of psychosis?*

Whereas the data summarized in my meta-analysis (**Paper 1**) indicated that there is an association between continued use of cannabis and risk of relapse in psychosis, this evidence is of a cross-sectional nature and, hence, does not allow to draw conclusions regarding the direction of effect. For instance, it has been proposed that the association could be the result of self-medication, i.e. those with more severe psychopathology are more likely to use the drug in order to relieve their symptoms (Khantzian, 1985). However, this theory is not supported by the findings from my thesis. First, **Paper 2** showed that those who used cannabis continuously (i.e. using cannabis in each month of the two years following the onset) were more likely to relapse. This means that in those users, the cannabis use preceded the relapse event. Furthermore the effect remained significant when controlled for onset illness severity (indexed as care intensity at onset). Together, these findings do not support the notion that continued cannabis use is a consequence of a relapsing/more severe illness course. Similarly, the results from the path analysis (**Paper 3**) indicate that continued cannabis use predicted risk of subsequent relapse, while the association was not significant in the reverse direction (increased cannabis use following the event of a relapse). Studies that have examined the issue of reverse causation in those with pre-existing psychosis report either a bi-directional relationship between cannabis use and symptom severity (Foti et al., 2010), or that frequency of cannabis use predicted an increase in subsequent psychotic symptoms, but not vice versa (Degenhardt et al., 2007; Henquet et al., 2010), indicating that reverse-causation in unlikely to explain the relationship between cannabis use and psychotic symptoms.

5. *Biological gradient: Does the effect of cannabis use on outcome reflect a dose-response relationship?*

If cannabis was a causal risk factor for relapse, one would expect that the risk increases with increasing doses of cannabis exposure. A dose-response relationship is supported by all three analyses carried out in my thesis. First, in the meta-analysis (**Paper 1**) I found that those who continued to use cannabis were at higher risk for relapse when compared to non-users and when compared to those who discontinued following the onset. Since those who discontinued using cannabis following the onset were not at higher risk for poor outcome when compared to non-users, the results implicate that a reduction of use may reduce the risk of relapse, although caution in warranted since this analysis did not control for important confounders. The increased risk linked to increased dosages of cannabis exposure could therefore reflect the increase in risk of accompanying confounders, e.g. if increased cannabis use goes hand in hand with poorer compliance with medication and/or increased use of other drugs. However, in **Paper 2**, in which I controlled for those confounding factors, I found that the highest risk for relapse and poor outcome remained significantly present in those with the highest dosage of cannabis exposure (daily use of skunk-type cannabis throughout the two years following the onset), while an increased risk of relapse was not present for who continued to use it but consumed milder forms of cannabis (hash-type), used it less frequently (less than daily), those used it only intermittently following the onset or those who had a history of premorbid cannabis use but did not use it following the onset. This finding suggests a dose-response relation, with the poorest outcome found in those users that were exposed to high doses of THC following the onset. Furthermore, premorbid cannabis use may have reversible effects with regard to psychotic symptoms, since patients with a history of premorbid regular use were not

different to those who never used it at a regular basis in their outcome. These results are therefore in accordance with epidemiological evidence of the adverse dose-dependent effects of cannabis and risk of relapse (Bergé et al., 2016; Hides et al., 2006; Linszen et al., 1994) and psychotic symptom severity (Degenhardt et al., 2007) and reversible effects of cannabis exposure following abstinence (Rabin et al., 2013). **Paper 3** is in further support of this, since within-subject change (increase) in pattern of cannabis continuation over time was linked to increased risk of relapse, while controlling for unobserved time-invariant sources of confounding (e.g. premorbid genetic profile) and observed time-variant sources of confounding (medication adherence, other illicit drug use). This is similar to what was found by studies looking at cannabis use as a risk factor for onset of psychotic symptoms. For instance, a within-subject increase in cannabis use over time increased the risk of development of psychotic symptoms (David M Fergusson et al., 2005). This is consistent with independent evidence from a study in chronic methamphetamine users without a comorbid diagnosis of psychosis, in which change in frequency of cannabis use was linked to the risk of presence of psychotic symptoms (McKetin et al., 2013). This is also in accordance with a study that employed a sibling-pair design to control for some of the shared genetic (<50%) and environmental influence by J. McGrath et al. (2010), which found that duration of cannabis use was a significant predictor of psychotic outcome in young adults. To summarise, my results are in favour of a dose-response effect that persists beyond the effect of confounding and cannot be explained by shared-vulnerability.

6. *Plausibility: Is there a plausible biological explanation for the link between cannabis use and exacerbation of psychotic symptoms?*

My results suggest that those who were exposed to the highest doses of THC had the highest risk for psychotic symptom exacerbation following the onset. In line with this, the administration of THC has been consistently linked to the production of acute transient psychotic experiences in healthy human individuals with minimal previous cannabis exposure (Sagnik Bhattacharyya, Atakan, et al., 2015b; D'Souza et al., 2008; Englund et al., 2015; P. Morrison et al., 2009; Radhakrishnan, Skosnik, et al., 2015; Tunbridge et al., 2015) and in those who are current regular users of cannabis (Van Wel et al., 2015). THC administration also triggered the exacerbation of psychotic symptoms in those with a pre-existing psychotic disorder (D'Souza et al., 2005), despite chronic treatment with DA D_2 receptor antagonists (D'Souza et al., 2005). At a neural level, cannabis may exerts its effects by causing functional changes in the brain structures implicated in the pathology of psychotic disorders, such as the striatum or midbrain (S Bhattacharyya et al., 2012; Sagnik Bhattacharyya, Falkenberg, et al., 2015; Sagnik Bhattacharyya et al., 2009; Bossong et al., 2009). However, the precise neurochemical mechanisms that underlie the psychotomimetic effects of THC are still relatively poor understood. For instance, most research has focused on the dopamine hypothesis as the underlying model of cannabinoid action (Kuepper et al., 2010). The hypothesis states that the emergence of psychotic symptoms, which are thought to derive from a state of aberrant salience, are the result of excessive stimulation of DA D_2 receptor proteins in the brain (Howes & Kapur, 2009; Kapur, Mizrahi, & Li, 2005). Although abnormalities in multiple pathways may lead to psychosis, including glutamate and GABA, abnormality in dopamine neurotransmission, particularly in striatal regions, is proposed to mirror the final common pathway leading to psychosis (Howes & Kapur, 2009). Hence, one would therefore expect cannabis use to be linked to changes in dopaminergic signalling. However, experimental evidence from human studies

investigating this mechanism of cannabis action is rather inconclusive so far [cf. Sami et al. (2015) for a systematic summary of studies]: One single photon emission tomography (SPECT) study did not find an effect of a low dose of THC (2.5mg IV) on striatal dopamine release, despite the presence of psychotomimetic properties of THC, suggesting that the striatal DA system may not mediate the psychoactive effects of cannabis (Barkus et al., 2011). This is similar to another position emission tomography (PET) study administering 10mg oral THC, which did not find an effect on striatal binding, despite inducing psychotic symptoms (Stokes, Mehta, Curran, Breen, & Grasby, 2009). Those findings would also imply an ineffectivity of DA D_2 blockers in preventing THC-psychosis, which was the case in one experimental study that reported that a D_2 receptor antagonists (e.g. Haloperidol) failed to prevent from the psychotomimetic effects following THC-administration (D'Souza et al., 2008) and one epidemiological study that linked onset cannabis use to antipsychotic treatment failure (Patel R et al., 2016). Another acute challenge study reported increases in positive symptoms following THC administration in psychotic patients treated with D_2 receptor-based antipsychotic medication (D'Souza et al., 2005). However, latter study did not include a non-medicated control group, for which reason it cannot be concluded as to whether the induced symptoms following THC administration where in fact blunted or not. Overall, those findings in humans are somewhat incongruent with the dopamine-hypothesis and are not supported by relatively consistent evidence from experimental studies in animals, in which THC increased dopamine levels in several brain areas such as striatal and prefrontal areas (Cheer, Wassum, Heien, Phillips, & Wightman, 2004; Ginovart et al., 2006; Kreitzer & Malenka, 2005; Tanda & Goldberg, 2003; Yin & Lovinger, 2006), increased central dopamine synthesis (Bloom, Johnson, & Dewey, 1978) and inhibited dopamine uptake (Poddar & Dewey, 1980). Nevertheless, some

evidence from human studies is in support of this; using PET and a dopamine D_2/D_3 tracer (raclopride), Bossong et al. (2009) reported that the tracer binding was modestly (~3%) but significantly decreased in the ventral striatum, implicating an increased release of endogenous dopamine in this region. However, it might be the case that significant effects of THC are more easily detectable in genetically predisposed individuals. For instance, a SPECT case study in a medication-free patient with psychosis reported a 20% decrease in striatal D_2 receptor binding ratio following exposure to THC, suggesting increased synaptic dopamine release underlying the THC-exacerbated psychotic symptoms (Voruganti, Slomka, Zabel, Mattar, & Awad, 2001). Another PET study reported THC induced dopamine release only in patients with psychosis and their unaffected siblings but not in healthy controls (Kuepper et al., 2013). This is consistent with observational evidence that did not find a link between cannabis use and risk for antipsychotic treatment failure in patients with psychosis (Crespo-Facorro et al., 2007; Rais et al., 2010). A more recent RCT in humans reported that haloperidol inhibited the symptom-inducing effects of THC (including positive and negative symptoms), as well as the cognitive impairments following the administration of THC in healthy subjects (Marieke Liem-Moolenaar et al., 2010), which would be in further support of the hypothesis that THC exerts its effect via increased striatal DA release. In latter study, THC administration also affected prolactin levels - a biomarker for dopaminergic activity – and this effect was ameliorated by haloperidol treatment (M Liem-Moolenaar et al., 2010). Finally, CB_1 blockers may be able to inhibit the psychoactive effects of excessive D_2 stimulation. For instance, there is evidence that CBD inhibited the psychosis-inducing effects of $_L$-DOPA (Zuardi et al., 2008) and a RCT comparing CBD with amisulpride reported equal effectivity between the two drugs in reducing psychotic symptoms (Leweke et al., 2012). It has therefore been suggested

that the antipsychotic effects of CBD stem from the attenuation of dopaminergic activity in brain.

To summarise, although the neurochemical mechanisms by which cannabis induces it psychotomemtric effects are still not fully understood, some evidence suggests that the psychotomimetic effects of THC are potentially partly mediated by striatal dopamine release – at least in individuals with a genetic pre-disposition for psychotic disorders. Despite the uncertainties regarding the exact underlying neurochemical mechanisms of THC action, there is robust behavioural experimental evidence in humans and animals that is in support of the notion that the main psychoactive ingredient of cannabis – THC – can acutely induce and exacerbate psychotic symptoms in a dose-dependent manner. Therefore, it seems plausible to presume that the association between continued cannabis use and increased risk of exacerbation of psychotic symptoms as found in my papers (**Paper 1, Paper 2, Paper 3**) reflects a pharmacological effect of THC on brain-chemistry in FEP patients.

7. *Confounding: Is the association between cannabis and relapse confounded by a third variable?*

The issue of confounding is one of the most heatedly debated topic within the research community interested in the epidemiology of cannabis use and mental health (Ksir & Hart, 2016b). For instance, cannabis users at onset of their first episode have been shown to be systematically different from non-users in various clinical and demographic measures (Baeza et al., 2009; L. Clausen et al., 2014; González-Blanch et al., 2015; González-Pinto et al., 2011; Patel R et al., 2016; B. Schimmelmann et al., 2012; Seddon et al., 2015) and those who continue using the substance following the onset are more likely to have an earlier age of onset of psychosis (González-Pinto et al.,

2011), use alcohol (González-Pinto et al., 2011) and other drugs (L. Clausen et al., 2014; Faridi et al., 2012; González-Pinto et al., 2011; Maria Isaac, Isaac, & Holloway, 2005a) and are non-adherent with their medication (Foglia et al., 2017). This is similar to the findings reported in **Paper 2**, in which I found that the different cannabis groups were significantly different with regard to medication adherence, other drug use and age of onset, for which reason those differences could play a role within the cannabis-relapse association. In the following section I therefore discuss the issue of confounding by looking at the role of various confounders that were highlighted in the previous literature, including:

a. Medication non-adherence: First, the results from **Paper 2** indicate that high frequency skunk use remained a significant predictor for outcome including risk of relapse, length of relapse, time until a relapse occurred and care intensity at follow up, when controlled for medication non-adherence (**Paper 2**). This is similar to other studies that found that medication adherence did not explain the link between continued cannabis use and risk for non-remission, illness severity of functioning at follow up (B. Schimmelmann et al., 2012). In accordance, a recent study also found that frequency of cannabis use was not confounded by non-compliance to medication (Bergé et al., 2016) and there is evidence that the diagnosis of CUD following the onset was linked to risk of readmission and risk of compulsory admission when medication adherence was taken into consideration (Sorbara et al., 2003). Adverse effects of cannabis use also persisted independent from medication adherence with regard to severity of positive symptoms (Faridi et al., 2012; Hides et al., 2006). Nevertheless, the magnitude of effect of continued cannabis use that I found in simple analyses (**Paper 2** and **Paper 3**) was reduced in the multiple analyses when medication

adherence was included as a covariate. To illustrate, the magnitude of effect identified in univariate analysis (OR 4.37, cf. **Paper 2**) dropped when medication adherence was included (OR 2.73, cf. **Paper 2**). Furthermore, considering that continued cannabis users were less likely to be adherent to their medication (e.g. **Paper 3**: 41% vs. 21% classified as full adherent in non-users vs. continued users) and the independent effect of medication adherence on risk of relapse, it is plausible that some of the effects of cannabis may have been mediated by non-adherence to antipsychotic medication in those who also use cannabis. This is in line with other follow up studies in FEP patients, which (i) showed that cannabis users are less likely to adhere to their medication (Foglia et al., 2017) and (ii) in which medication non-adherence predicted risk of relapse (Barbeito et al., 2013; Caseiro et al., 2012; Coldham et al., 2002; Gearing et al., 2009; Michele Hill et al., 2010; Hui et al., 2013; Martin Lambert et al., 2010; Levy et al., 2012; Morken et al., 2008; Üçok et al., 2006; H Verdoux et al., 2000), involuntary readmission (H Verdoux et al., 2000), as well as number of days spent in hospital, number of hospitalisations and days under section (Morken et al., 2008). In fact, medication non-adherence remained the strongest predictor for relapse when considered in multifactorial prediction models (Caseiro et al., 2012). Finally, my finding that adherent patients exposed to high doses of THC remain at higher risk for poor outcome is in line with studies implicating an ineffectiveness of antipsychotic treatment in reducing cannabis-induced psychotic symptoms, e.g. experimental evidence reporting an exacerbation of psychotic symptoms following THC administration in patients treated with antipsychotic medication (D'Souza et al., 2005), the finding that haloperidol did not reduce the psychotogenic effects following THC

administration (D'Souza et al., 2008) and observational evidence supporting a link between onset cannabis use antipsychotic treatment failure (Patel R et al., 2016). However, evidence in this regard is mixed, since there is experimental evidence that haloperidol was in fact effective in inhibiting the THC-induced symptoms (Marieke Liem-Moolenaar et al., 2010) and the absence of a link between cannabis use and antipsychotic treatment failure (Crespo-Facorro et al., 2007; Rais et al., 2010).

In summary, instead of concluding "*FEP patients with an active cannabis use disorder may make a choice of either stopping cannabis and not taking medications or continuing cannabis but becoming more adherent to medications*" [(Faridi et al., 2012), Abstract], it seems rather crucial to promote both abstinence from (high-potency) cannabis in combination with medication adherence as the more optimised treatment approach with regard to relapse prevention.

b. Other substance use: Although cigarette use and illicit drug use had some adverse effects on outcome (cf. **Chapter 6.1** "*3. Specificity*" for a more detailed discussion on the effects of the different substances), my results indicate that the effect of continued cannabis use and changes in cannabis use remained independent predictors for risk of relapse (**Paper 2** and **Paper 3**). The independent contribution of cannabis use on outcome when controlled for other substance use is in line with follow up studies in which the effect of cannabis use on outcome in FEP patients and patients with established psychosis, such as relapse (D. van Dijk, M. W. Koeter, R. Hijman, R. S. Kahn, & W. van den Brink, 2012a) and positive symptom severity (Degenhardt et al., 2007; Foti et al., 2010; González-Pinto et al., 2011; Henquet et al., 2010), as well as studies

that reported that frequency of cannabis use remained a significant predictor for onset of psychosis (Di Forti, Marconi, et al., 2015) and symptoms severity in the general population (David M Fergusson et al., 2005; J. McGrath et al., 2010), independent from other drug use.

c. "Shared-vulnerability": Besides the potential confounding effect of the factors outlines above, the most recent debate is concerned with the "shared-vulnerability" hypothesis, which proposed that the association reflects the result of a (genetic) liability for both cannabis use and the risk of developing psychosis (Ksir & Hart, 2016a). For instance, there is evidence for a genetic contribution to the initiation of cannabis use, as well as evidence indication genetic overlap between cannabis initiation and problematic use of cannabis (Verweij et al., 2010). If there was a "shared-vulnerability" this genetic vulnerability for problematic cannabis use would then overlap with the vulnerability for psychosis. While there is some evidence suggesting the presence of some genetic risk for both cannabis use and onset of psychosis (J. Boydell et al., 2007; McGuire et al., 1995; R. A. Power et al., 2014; Proal et al., 2014), other studies suggest that a full genetic confounding effect is unlikely to be the case and that – if any genetic confounding exists – it would explain only a small proportion of the association between the two (Andréasson et al., 1989; Di Forti, Vassos, et al., 2015; Sherva et al., 2016b).

Addressing the potential confounding effect of the genetic profile has been carried out in **Paper 2** by taking into consideration family history of mental illness and in **Paper 3**, in which I used fixed effects models to control for the premorbid genetic profile. First, in **Paper 2**, I found that the different cannabis groups were not significantly different with regard to their family history of

mental illness. Based on the shared-vulnerability hypothesis, it can be hypothesized that those patients who continued using cannabis in a high-frequency and high-dose (skunk-like) manner (i.e. those who were at highest risk for the experience of a relapse) would also have the highest genetic load when compared to never regular users/former regular users, which was not the case (p=0.61, cf. **Paper 2**: e.g.. 48% vs. 55%/44% that had a family history of a mental disorder). Problematically, the factor family history of mental illness may not fully capture the effect of "shared-vulnerability". In fact, it has been suggested that an "*unequivocal proof of cannabis exposure causing psychosis would require the experimental manipulation of cannabis use, with other confounding factors controlled for by random assignment of participants to different groups*" [cf. Ksir and Hart (2016a), Page 3, Paragraph 4]. For this reason, **Paper 3** adopted the sibling design approach – a quasi-experimental design – in which the same subject was used as its own control by comparing periods of non-exposure to cannabis to periods of exposure to cannabis. The results suggest that the risk of relapse was higher in periods of exposure, which was present in a dose-dependent fashion for level of continuity of use and while controlled for medication non-adherence and other illicit drug use. Although a genetic contribution might have attenuated the effect, these results clearly indicate that premorbid genetic confounding cannot explain the relationship between cannabis and risk of relapse. This is in accordance with other studies using such design, in which changes in frequency of cannabis use were linked to increases in psychotic symptoms in a population sample (David M Fergusson et al., 2005), a sample of methamphetamine abusers (McKetin et al., 2013) and evidence from an FEP sample, which showed that patients were characterised by

higher positive symptoms in periods of cannabis use when compared to periods of non-use (Foti et al., 2010).

d. Ethnicity: Differences in ethnicity did not confound the effects of continued cannabis on risk of relapse, neither when included as a covariate in multiple regression models (**Paper 1**), nor when considered as a time-invariant unobserved source of confounding in fixed effects analysis (**Paper 2**). However, non-white ethnicity independently predicted an increased risk of relapse, more numerous relapses, longer hospital stays, a shorter time until a relapse occurred and higher care intensity at follow up, implicating that this factor is an independent risk factor for poor outcome (**Paper 1**). This is in accordance with the finding that patients of black minority were more likely to relapse and to be detained under the mental health act throughout following their onset (N. Goater et al., 1999). The link with poorer outcome in this group may be discussed in the context of findings of an excess of psychotic disorders in migrant populations and minority ethnic groups. For instance, an early report noted that hospitalisation rates for psychosis were higher in Norwegian emigrants to the US (Minnesota), when compared to the Norwegian population in Norway or the American population born in America (Odegaard, 1932). Those trends have been replicated in subsequent studies (Cantor-Graae, Pedersen, McNEIL, & Mortensen, 2003; Selten et al., 2001), and there has been a particular interest in the high incidence rates among black Caribbean's in the UK. For instance, a meta-analysis reported that the rates of schizophrenia were increased in various ethnic minority groups when compared to the (white) British population, including black Caribbean (RR 5.6), black African (RR 4.7) and Asian (RR 2.4) (Kirkbride et al., 2012). Several hypotheses have been proposed that might

explain the link with schizophrenia and could serve as a potential explanation as to why the non-white ethnic group in my sample was at risk for poor outcome, such a predisposition to psychosis in the first generation of migrants or socio-environmental factors linked to the migration process and post-migratory experiences [cf. Kirkbride et al. (2012) for details]. Although it was beyond the scope of my thesis to further explore on those mechanisms, theories proposing that the increase in risk stems from higher rates of substance abuse in ethnic minorities, or gender and age differences (Kirkbride et al., 2012) are not in accordance with my findings, since the factor ethnicity remained an independent predictor when controlled for cannabis use and other illicit drug use, as well as gender and age of onset.

e. Diagnosis at onset: Neither were the rates of relapse significantly different between those with an onset diagnosis of affective psychotic disorder to those with a diagnosis of non-affective psychotic disorder, nor was the factor onset diagnosis (affective vs. non-affective) a predictor for any of the other outcomes that were assessed in my thesis (**Paper 2**). Furthermore, the different cannabis groups did not differ in their onset diagnosis, implicating that differences in diagnoses may not play an important role within the association between continued cannabis use and relapse. This is in line with other studies that did not find that diagnostic heterogeneity significantly predicted risk of relapse following the onset (Bergé et al., 2016; Castine et al., 1998; Gearing et al., 2009; Levy et al., 2012; Tarricone et al., 2014)

f. Onset severity: Onset severity as indexed as care intensity at onset was independently linked to risk of relapse but did not confound the relationship, which is supported by other studies that found an increased risk of relapse

predicted by onset clinical characteristics, including higher illness severity (D. Addington et al., 2010; Alvarez-Jimenez et al., 2011; Barrowclough et al., 2015; Möller et al., 2002; Üçok et al., 2006), lower level of functioning (D. Addington et al., 2010; Gearing et al., 2009; Üçok et al., 2006), poorer cognition at onset (Stirling et al., 2003) and longer duration of hospitalisation at onset (Hui et al., 2013).

g. Age of onset: Cannabis use status following the onset was significantly linked to age of onset of psychosis, in which case continued cannabis users comprised the group with the youngest age of onset, which is in accordance with previous studies (González-Pinto et al., 2011; Maria Isaac et al., 2005a). Although some studies reported that an earlier age of onset was significantly linked to greater risk of relapse (D. Addington et al., 2010; Alvarez-Jimenez et al., 2011; Caseiro et al., 2012; Chi et al., 2016; Levy et al., 2012; A Malla et al., 2008; Üçok et al., 2006) and longer durations of relapse (Lenior et al., 2005), my results do not suggest that this factors had an independent contribution that was beyond the effect of cannabis use, ethnicity, onset illness severity and medication adherence.

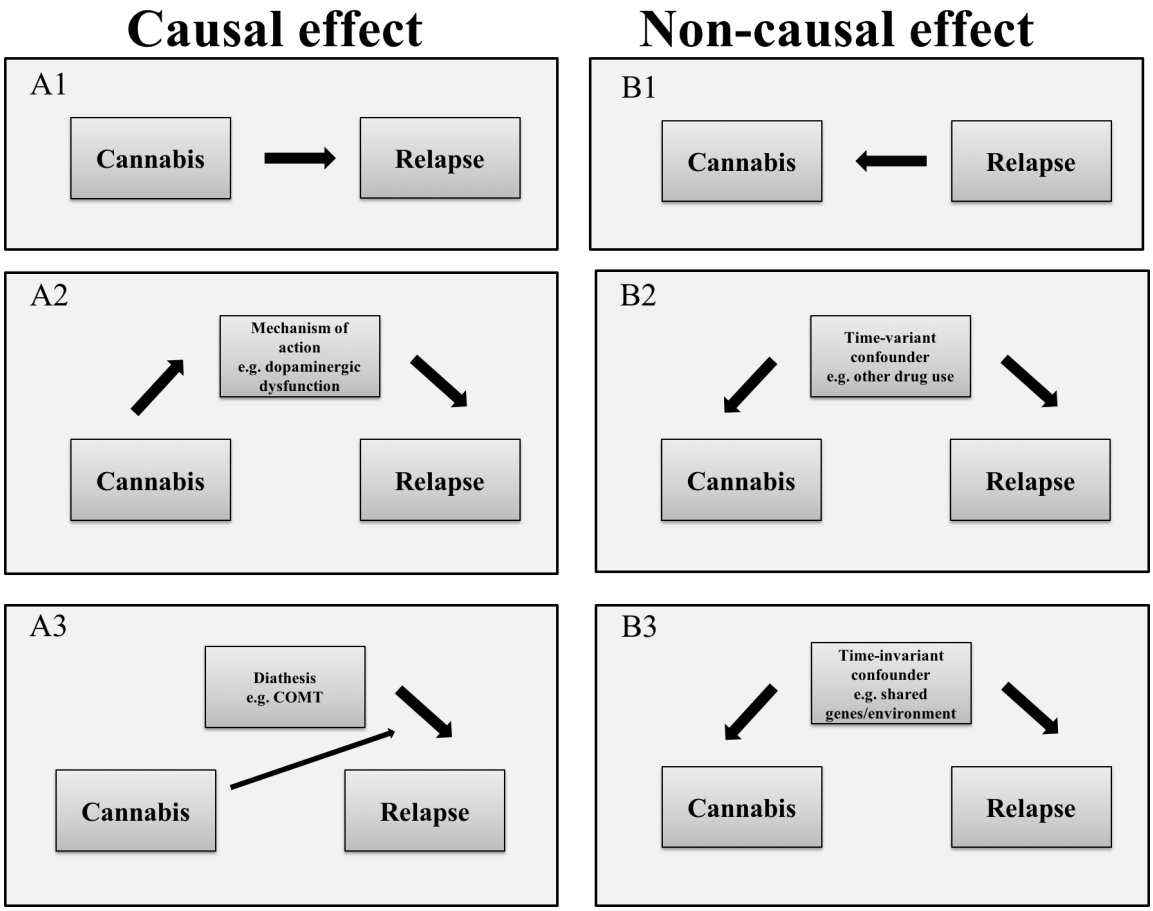
h. Gender: Gender did not significantly increase the risk of relapse, i.e. the risk of relapse was comparable between men and women. This is in line with the majority of studies looking at relapse in FEP patients, in which no significant effects of gender was reported (D. Addington et al., 2010; Chi et al., 2016; Lenior et al., 2005; Levy et al., 2012; A Malla et al., 2008; Tarricone et al., 2014; Wiersma et al., 1998). Although the male patients in my sample were more likely to continue using cannabis following the onset, which is consistent with previous studies (L. Clausen et al., 2014; Moore et al., 2012; Patel R et al.,

2016; Van Mastrigt et al., 2004), gender did not confound the effects continued cannabis use on risk relapse and related outcome. However, my analysis does not rule out that gender differences may moderate the effects of cannabis. For example, there is evidence suggestive of a dopaminergic sensitivity in the male brain when compared to the female one, in which case hormones such as oestrogen may play a protective role (Munro et al., 2006). Future research should therefore investigate gender-related sensitivities to cannabis use following the onset.

To summarise, my results provide a solid ground to conclude that continued cannabis use has adverse effects on risk of relapse and related outcomes that are likely be causal in their nature. As shown in *Figure 18.* (cf. below), several mechanisms have been proposed that would explain the association between continued cannabis use and relapse. Hence, my results are in favour of a causal link between cannabis and relapse (Model A1, Model A2, Model A3), although based on my findings it is not possible to draw conclusions regarding the precise mechanisms of cannabis actions (Model A2), or the modulating effects of individual vulnerabilities (Model A3) in response to cannabis exposure. Within the wider literature, my findings are in accordance of a dose-response relationship between cannabis and psychotic symptoms in observational studies (Di Forti, Marconi, et al., 2015; David M Fergusson et al., 2005; Foti et al., 2010; J. J. McGrath et al., 2015) and laboratory-based studies (D'Souza et al., 2005; D'Souza et al., 2008; Marieke Liem-Moolenaar et al., 2010), an effect of cannabis use on brain function and chemistry (S Bhattacharyya et al., 2012; Sagnik Bhattacharyya, Falkenberg, et al., 2015; Sagnik Bhattacharyya et al., 2009; Bossong et al., 2009), a temporal relationship in which cannabis use is a preceding factor prior to the adverse outcome and is not the result of reverse causation (opposing Model B1) (David M

Fergusson et al., 2005; Foti et al., 2010; Henquet et al., 2010) and an independent effect that cannot be explained by potential confounders such as medication non-adherence, other illicit drug use (opposing Model B2) or a "shared-vulnerability" (opposing Model B3) (Foti et al., 2010; J. McGrath et al., 2010).

Figure 18. Mechanisms linking continued cannabis use to risk of relapse



Note. Adapted from Agrawal and Lynskey (2014): Mechanisms that may link continued cannabis use to risk of relapse, including causal effects of cannabis as shown in model A1[Cannabis use directly causes relapse], A2[Cannabis causes relapse via alterations in biological/environmental pathways] and A3[Cannabis causes relapse, while being modified by gene-environment interaction/environment-environment interaction)] and non-causal effects of cannabis as shown in model B1[Reverse causation, such as self-medication], B2[Confounding by time-invariant factors such as other illicit drug use] and B3[Confounding by premorbid shared genes/environment].

6.2 IMPLICATIONS

6.2.1 CLINICAL IMPLICATIONS

When assuming that continued cannabis use has a causal effect on risk of relapse within the first two years following onset of psychosis, this has important clinical implications. First, the results indicate that it is the continued high-frequency use (predominantly daily use in all 24 months) of high-potency cannabis ("skunk-like"), as well as the increase in cannabis continuation over time that links the substance to poor outcome. Since I provide evidence that former regular users who stopped after onset had the most favourable illness course with regard to relapse, the main interventional goal would therefore be to reduce cannabis use following the onset as early as possible in order to limit the progression to a more severe and treatment resistant form of illness. Early intervention is particularly important since, according to the "critical period" hypothesis (Birchwood et al., 1997), FEP patients may benefit the most especially in those first few years of their illness. Changes in cannabis use therefore comprise a crucial intervention target in those early stages of the illness. Considering that the proportion of cannabis users who started using cannabis following the onset of psychosis but had no history of premorbid regular use in my sample was relatively low (1.3%), this would implicate that there is no urgent need for early intervention services to focus on the implementation of novel treatments that aim to prevent the incidence of cannabis use following the onset, since this seems to be only rarely the case. Instead, since reductions in cannabis use may represent one of the most preventable causes of relapse, interventions may focus on persuading those who use cannabis when presenting with their first episode psychosis to reduce their use or shift to less potent forms of cannabis following their onset. Although there are numerous observations that indicate a naturalistic reduction following the onset (~ 46%, cf. *Figure 9*., **Chapter 2.6**), a large

proportion of patients continue to use cannabis (~ 46%, cf. *Figure 9*., **Chapter 2.6**) and cannabis remains the preferred drug of use and abuse within substance using patients (Lange et al., 2014; Levy et al., 2012; D Wade et al., 2006). Discouragingly, none of the available treatments to date has been effective in treating comorbid cannabis use, either when targeted in psychological interventions (Christine Barrowclough et al., 2014; Bonsack et al., 2011; Hjorthøj et al., 2013) or by means of pharmacological treatments (Wilson & Bhattacharyya, 2016). Since cannabis use – especially if used in a frequent manner such as daily – has established itself as an important activity in the patients everyday life, it is of crucial importance to better understand the biological and psychological mechanisms linked to continued cannabis use in order to develop more effective interventions.

6.2.2 Implications for future research

The accumulation of evidence proposing a risk factor such as continued cannabis use as a causal factor for risk of relapse reflects only the first step in epidemiological research aiming to develop personalized prediction models for outcome in FEP patients. Cannabis use represents only a small part of a more complex scene. Based on the findings from my thesis, several lines of research should now carry out further investigations, in which (1) the precise mechanisms of actions are further explored, which would allow the development of novel and specialized intervention methods (cf. *Figure 18.*, Model A2), (2) the issue of sensitivities to the effects of cannabis is further explored (cf. *Figure 18.*, Model A3), which would allow to identify individuals that are at the highest risk for the adverse effects of cannabis and thereby help to develop personalised algorithms that can be implemented in clinical practise and

guide clinicians in their decision making, and (3) look at a wider range of outcomes in the context of continued cannabis use in FEP patients:

(1) First, with regard to the mechanisms by which cannabis increases the risk of relapse, this question has not yet been extensively investigated in clinical research looking at a brain, genetic or environmental level. For instance, from a biological perspective, it has been suggested that cannabis may lead to treatment failure of antipsychotic medication and thereby increases the risk for relapse (Patel R et al., 2016). Further studies should therefore focus on neurotransmission systems implicated in the psychopathology of schizophrenia such as dopamine, glutamate and the endocannabinoid system. Those findings would contribute to a better understanding of the neurobiological basis of cannabis action, which would help developing novel pharmacological treatments that aim to reduce cannabis use as well as cannabis-induced symptoms in patients with psychosis. There is also a huge unmet clinical need for individualised effective psychological treatments for patients with psychosis with a comorbid cannabis use disorder, considering recent attempts that failed to reduce cannabis use in patients with psychosis (Christine Barrowclough et al., 2014; Bonsack et al., 2011; Hjorthøj et al., 2013). Hence, developing a deeper understanding regarding the reasons and motivations for cannabis use may allow the conceptualisation of more effective and tailored psychological intervention programs. Although studies have attempted to investigate reasons for use in patients with psychosis, in which they reported a need for “relaxation”, “feeling high” or “becoming intoxicated” as the most commonly reported reasons for use (Pérez-Solá, 2014), this evidence does not easily lend itself to the development of

interventions to reduce/ limit continued cannabis use among patients with psychosis. Given the recent technological advances, new methods such as ecological momentary assessment techniques such as experience sampling method (ESM) may allow the capture of richer longitudinal data in real-time during the course of daily life on the state- and context-sensitive determinants of cannabis use preferences, experiences and reasons for continued cannabis use. The longitudinal assessment of cannabis use in my thesis has demonstrated its methodological superiority over cross-sectional investigations by looking at within-person differences in addition to between-person differences, and the applications of such design in a real-life context might have the potential to provide a deeper understanding into the mechanisms that may underlie the maintenance of cannabis use in patients with psychosis.

(2) Second, another important area of future research lies in identifying vulnerable individuals to the effects of cannabis in order to better provide individualized risk models based on the person's clinical presentation and/or biomarker when presenting to the psychiatric services. This would contribute towards refined prediction models within the approach of personalized medicine, which should in turn lead to more economic and efficient treatment approaches. To illustrate, evidence suggests that (i) the risks associated with cannabis use may be higher if consumed during sensitive developmental periods (Arseneault et al., 2002; Di Forti et al., 2014; Malone, Hill, & Rubino, 2010) in which the brain is likely to be more sensitive to environmental insults, (ii) is dependent on the genetic profile of the person (S Bhattacharyya et al., 2012; D'Souza et al., 2005; Henquet et

al., 2004; Tunbridge et al., 2015; van Winkel, Genetic, & Outcome of Psychosis, 2011), and (iii) may show interactive effects with childhood adversity and recent life events (Craig Morgan et al., 2014; Murphy, Houston, Shevlin, & Adamson, 2013). Therefore, sensitivities to cannabis might be present in form of multiplicative (Zammit, Lewis, Dalman, & Allebeck, 2010) or synergistic models (Van Os, Rutten, & Poulton, 2008) as previously suggested, which has yet to be investigated in prediction models looking at relapse and related outcome in first episode psychosis. Furthermore, a deeper understanding on pharmacological modulators of cannabis action in psychosis is crucial for policy makers and health care providers, e.g. regarding the precise effects of changes in frequency of use or change in cannabis type (e.g. from skunk-type to hash-type cannabis). Especially since the number of countries in which cannabis has been legalised or is likely to be legalised in the future has risen, whereby cannabis becomes freely available to buy and to sell, questions on regulation issues may become more important than issues around criminalisation. Therefore, it seems particularly important to provide a deeper understanding on dose-response relationships (especially the effect of the potency of the cannabis consumed) in the context of mental health. Hence, future studies should look more in detail on the THC:CBD ratio as a measure of potency of the cannabis consumed in patients with psychosis, e.g. by close monitoring using saliva (C. J. Morgan et al., 2010) or hair samples (Hermann et al., 2007). This would provide a much richer pool of information regarding the effect of the potency of the cannabis consumed. Finally, since the recreational use of synthetic cannabis has increased in recent years (Wells &

Ott, 2011), future studies should also investigate the effects of this cannabis product in FEP samples, which was not possible in my thesis due to the absence of users that consumed synthetic cannabis.

(3) Despite the fact that the data extracted from the clinical records is a reliable source for hospitalisation data, which allowed me to look at different but related measures of relapse, including number of hospitalisations, length of hospitalisation, time until a hospitalisation occurred and intensity care at follow up, I did not investigate the effects of changes in cannabis use on other mental health outcomes such as changes in cognition, depression, anxiety, or functioning – outcomes which have rarely been included in longitudinal studies in FEP samples, for which reason current knowledge is limited regarding the contributing role of continued cannabis use in this context. Considering that I found evidence suggesting that continued cannabis use may lead to cognitive impairments (Schoeler & Bhattacharyya, 2013; Schoeler et al., 2015), mood and affective symptoms (Schoeler et al., under review), as well as deviant behaviour (Schoeler, Monk, et al., 2016) over the life-span, future longitudinal studies in FEP patients should therefore include multiple outcomes in order to compare the effects of cannabis use over time directly across the different outcomes.

6.3 STRENGTHS

One of the main strength of my investigation is its design as a follow up study of a cohort of patients that were all at the same stage of illness when recruited for inclusion, namely their first episode psychosis (therefore untreated with anti-psychotic medication for an episode of psychosis, no previous contact with health services for psychosis), i.e. this group of patients comprised a homogeneous group with regard to treatment history for psychosis. Furthermore, I used a fixed period of precisely two years of follow up for all variables of interest, including the relapse and outcome data derived from clinical records, as well as all data collected via face-to-face interviews. I focused on this early stage following onset of psychosis as this is considered as the "critical period" that determines long-term outcome in psychosis (Birchwood et al., 1997). Using such a design addressed one of the main limitation from previous studies looking at cannabis use and relapse, in which patients were at different stages of their illness and cannabis using patients differed in their follow up durations from non-users, which could have led to bias in the results (Schoeler, Monk, et al., 2016).

Furthermore, in this study, I used a reliable measure of relapse, defined as readmission to hospital. This can be extracted from clinical notes using data on hospital admission. Using the WHO life chart, this method has been shown to provide reliable results for outcome that is prospectively assessed in schizophrenia (Susser et al., 2000a). This relapse definition has been suggested as a valid measure for relapse (D. E. Addington et al., 2012), that is universally applicable (Burns, 2007), captures high rates of relapse that base on clinical judgement (D. E. Addington, Patten, et al., 2013; Almond et al., 2004) and that is comparable to other follow up studies since it remains the most commonly employed operationalization (J. F. M. Gleeson et al., 2010).

Finally, another important advantage of my study is that information on cannabis use as well as other patient data such as medication adherence and other substance use was collected via face-to-face interviews (or phone-interviews for a subset of patients that could not appear in person), which was further validated by screening each patient's clinical records. With regard to the assessment of cannabis use, this approach made it possible classify patients into cannabis use groups based on their use patterns following their onset, taking into account parameters such as frequency of use, continuation of use, premorbid cannabis use, type of cannabis and changes in cannabis over time, which addresses limitation from previous studies that classified cannabis users based on relatively crude approximations with regard to ongoing cannabis use following the onset of illness. For instance, the non-consideration of cannabis use following the onset when looking at relapse may explain some of the inconsistencies in those studies that assessed cannabis use only at onset or looked only at lifetime cannabis use and outcome in FEP (Batalla et al., 2013b; Kivimies et al., 2016; Koenders et al., 2014; Lenior et al., 2005; Manrique-Garcia et al., 2014c; Patel R et al., 2016) . Other studies relied on clinical register based information only, which hinder to extract a more detailed account of cannabis use patterns (Manrique-Garcia et al., 2014b; Patel R et al., 2016; Grant E Sara, Philip M Burgess, Gin S Malhi, Harvey A Whiteford, & Wayne C Hall, 2014a). Although my approach comprises the limitation that refuser are not included in the follow up sample, I was thereby able to collect data on other time-varying information. Hence, given the large pool of collected covariates, I was able to control for a comprehensive amount of confounders that were previously not collectively considered in follow up studies exploring the relationship between cannabis use and outcome in FEP. The number of variables included in my analysis, as well as the fine-grained classification of the different cannabis groups was only possible

due to the large sample size of the study, which is one of the largest follow up studies in the context of this research question.

6.3 LIMITATIONS

Sampling issues

It has been highlighted that threat to causality is the problem of bias (e.g. with measurements and/or sample selection), which could lead to incorrect estimates in risk prediction models (Suzanne H. Gage et al., 2016). First, the sample followed up comprised patients with a first episode psychosis presenting for the first time to psychiatric services in south London. Since most the patients included were admitted to hospital around the time of onset (78%), out of which about 60% required admission under section, the majority of the sample comprised individuals that are more likely to suffer from an acute/severe form of their first episode compared to those who were only referred to the community mental health teams or home treatment teams (22% of the sample). Furthermore, relapse was defined as admission to hospital, which captures only the more severe relapse episodes rather than exacerbations that can be managed within the community. Nevertheless, the use of rating scales may result in too inclusive criteria, leading to over-estimation and non-comparability of relapse rates reported by the studies (Suzuki et al., 2014). Furthermore, all patients were well enough to complete the baseline assessment around the time of their onset and to take part in a face-to-face or telephone interview at follow up. Another issue may lie in the fact that the date of first presentation to the psychiatric services for psychotic symptoms does not necessary reflect the onset of first symptoms and, hence, duration of untreated psychosis (DUP) could have affected the results. Although I did not control for DUP psychosis in my multiple prediction models (**Paper 2**), the within-subject analysis (**Paper 3**), in which premorbid confounding factors were controlled for did not indicate that this factor acted as a confounder that would explain the association between continued cannabis use and risk of relapse. Independent evidence is also not indicative that DUP is a significant risk

factor for relapse (D. Addington et al., 2010; Caseiro et al., 2012; T. J. Craig et al., 2000; Levy et al., 2012; Tarricone et al., 2014; Üçok et al., 2006). Finally, as in any longitudinal study, I cannot rule out that this sample may comprise a selective subset of inner city first episode patients, which may limit its generalizability to services in more rural areas or areas outside of the UK. However, the rate of hospitalisation due to psychotic relapse in my sample (37% within two years following onset) is comparable when compared to hospitalisation data reported by other two-year follow up studies, including Canada (33% relapsed) (D. Addington et al., 2010), China (33% relapsed) (E. Y.-H. Chen et al., 2005), Denmark (39% relapsed) (Bertelsen et al., 2009) and US (56% relapsed) (T. J. Craig et al., 2000).

As another limitation inherent to follow up studies in such populations, a proportion of patients refused to take part in follow up assessments (n=117), which could have biased the results if the relationship between cannabis use and relapse was dependent upon being a refuser or a participant, i.e. I cannot rule out the possibility that follow up data on cannabis use and relapse outcome was missing not at random (MNAR). However, I investigated whether being a participant (Completer) or not (Refuser) may have affected the relationship between cannabis use prior to the onset of psychosis and relapse. Data on relapse was collected for those who refused by extracting this information from their clinical notes. The results indicate that the risks of relapse were comparable in cannabis users across the two groups (Completers and Refusers). Furthermore, I compared those who participated in the follow-up with those who refused on several baseline measures, including premorbid cannabis use, age of onset of psychosis, ethnicity and gender, which revealed that there were no significant differences. Furthermore, the potential limitation of bias due to refusal may not be an issue in the fixed-effects analysis employed **Paper 2**, in which individuals where used

as their own controls (period of exposure vs. period of non-exposure), whereby all premorbid existing group differences were controlled for.

Finally, it might be criticized that I included a heterogeneous group of patients that comprised all psychotic diagnoses, including affective and non-affective psychosis. Nevertheless, my thesis aimed to investigate the effect of cannabis use on risk of relapse regardless of the categorical diagnosis. Furthermore, the factor diagnosis (affective vs. non-affective) was not significantly linked to relapse, nor was it significantly linked to the different classifications of cannabis use, implicating that differences in diagnosis are unlikely to play a role in this association. This is in line with previous evidence that did not report an association between type of diagnosis and risk of relapse (Bergé et al., 2016; Levy et al., 2012; Tarricone et al., 2014) or a link between type of diagnosis and cannabis use in patients with psychosis (Baeza et al., 2009; Elkins, 2004; B. Schimmelmann et al., 2012).

Issues regarding the retrospective assessment of relapse-predictors

Some limitations need to be outlined that refer to the nature of the retrospective nature of the assessments, as it was done to gather information on cannabis use patterns within the two years following the onset. Although this may have resulted in recall bias due to memory problems, my cannabis data is not indicative of this. For instance, to assess the reliability of the retrospective assessment of cannabis use, I compared data for n=207 subjects on premorbid cannabis use (ever used before onset) collected at onset of psychosis with data on premorbid cannabis use reported at follow up. In 92.8% of those compared, reporting of premorbid cannabis use was consistent across both assessments (i.e., at onset and at follow-up); 4.8 % those who denied premorbid use when assessed at the onset of psychosis admitted it when re-examined at the follow up

assessment, while 2.4% denied pre-morbid cannabis use at follow-up assessment although they had admitted use when assessed at onset. Furthermore, questions about cannabis use were asked in a face-to-face interview (telephone) instead of a self-completion of questionnaires. I also chose a categorical approach in which cannabis users were grouped based on broader categories (e.g. by asking "Did you use cannabis at least once in each of the 24 months following the onset?" to classify a person as a continued user) rather using continuous (numerical) measures such as the cumulative number of joints smoked within the two years following the onset, which might be more susceptible to recall bias. Alternatively, it might be argued that cannabis use was underreported. However, interviews were conducted in research facilities and not within the clinical setting, while reinsuring the patient that this data was anonymized and only used for research purposes, for which reason patients may be more open to admit to their cannabis use. For instance, comparing the rates of self-reported cannabis use with the results from urine drug screens revealed a high overlap (94%) in previous investigations (Di Forti et al., 2014). Another potential limitation may lie within the assessment of type of cannabis, in which case I relied fully on information reported by the patients in order to separate "high-potency" (skunk-type) cannabis users from "low-potency" (hash-type) cannabis users, instead of using more biological measures such as the THC:CBD ratio derived from saliva (C. J. Morgan et al., 2010) or hair samples (Hermann et al., 2007). Nevertheless, the grouping of "skunk-type" and "hash-type" was done according to the characteristics of the cannabis samples collected by the Police in South East London, in which skunk-type was found have an average of 17% THC (and virtually no CBC), compared with 4% THC present in hash-type cannabis (Potter et al., 2008).

It is also important to mention that medication adherence was assessed using rather crude measures by rating a patient's adherence as either full, partial or non-adherent within the two years following the onset, based on their average range of percentage of missed appointments. In this context, it would be more informative to have close regular monitoring that would allow the inclusion of a more fine-grained measure of adherence, e.g. in form of the quantitative dosage of antipsychotic medication that was missed. Furthermore, based on my classification of medication adherence, it cannot be concluded as to whether medication non-adherence was a preceding factor prior to cannabis use/relapse or an event that followed cannabis use/relapse. Nevertheless, the scope of my thesis was not the systematic evaluation of the causal (temporal) effects of medication non-adherence as a risk factor for relapse/cannabis use, but mainly to control for its effects within the cannabis-relapse prediction model, which I have done in my analyses.

Issues regarding uncontrolled sources of confounding

First, while the effects of time-invariant sources of confounding was not be an issue in **Paper 3**, in which all premorbid sources of cofounding were controlled for, time-varying factors such as changes in the environment (e.g. life events), post-onset genetic changes (e.g. epigenetics) or changes in the treatment of antipsychotic medication could still have affected the results. However, this seems unlikely to be the case; With regard to life events, there evidence that cannabis remained a significant predictor for psychotic experiences (Craig Morgan et al., 2014) when controlled for this factor. In fact, evidence is more in favour of interactive effects of life-stress and cannabis use on psychotic symptoms rather than a confounding effect (Craig Morgan et al., 2014). Although it is important to be aware of epigenetic phenomena in this context,

this factor may not play a crucial role in my prediction models, since my outcome was defined as relapse within the first two years of the illness – a relatively short period in which environmental induced changes in an individual's genetic expression may not be strong enough to have an impact on outcome. Although change in medication is common following onset [e.g. mean number of antipsychotic medications prescribed following the onset was reported to be ~1.90 within the first two years of illness (Patel R et al., 2016)], there is little evidence to suggest that there are differences in efficacy between individual antipsychotic medications with regard to relapse prevention (Stefan Leucht et al., 2003).

Second, one limitation comprised by **Paper 2** is that some additional plausible confounding factors were not included in my prediction models. For instance, other relevant factors may include level of (premorbid) IQ, history of childhood adversity, duration of untreated psychosis and a more detailed assessment of dose-response relationships for different types of illicit drugs as well as for cigarette and alcohol use. However, those factors are most likely to contribute within an environment x environment interaction with cannabis use (cf. Model A3, *Figure 18.* above) rather than as full confounders. For instance, interactive effects with cannabis in predicting psychotic experiences have been reported with regard to childhood adversity and trauma (Craig Morgan et al., 2014; Murphy et al., 2013) and frequency of other illicit drug use (McKetin et al., 2013). In this context, little evidence is in support of a non-causal link between cannabis use and psychosis due to non-adjustment of those factors, which is indicated by studies that found that the association between cannabis and emergence of psychotic experiences or exacerbation of psychotic symptoms persisted when controlled for premorbid IQ (David M Fergusson et al., 2005), childhood adversity (Henquet et al., 2004; Craig Morgan et al., 2014), frequency of other illicit drug use (Di Forti et al.,

2014; David M Fergusson et al., 2005; Foti et al., 2010; Henquet et al., 2004) and frequency of cigarette use (Di Forti et al., 2014; David M Fergusson et al., 2005), as well as duration of untreated psychosis (Sorbara et al., 2003). Hence, the exclusion of those factors in the risk prediction models is unlikely to have affected the results.

Issues in the statistical reporting

First, it might be criticized that I did not report Bonferroni-corrected *p*-values in the multiple analysis carries out in **Paper 2**, in which 5 different prediction models were evaluated. However, there are potential issues associated with the indiscriminate use of Bonferroni-correction (Perneger, 1998), for which reason the choice of whether or not to make corrections for multiplicity is best decided according to the importance of the threat of type 1 or type 2 errors in the current investigation. In the present investigation, it seems that a type 2 error (accepting the null hypothesis although continued cannabis use is associated with a greater risk of relapse of psychosis compared to non-use) is of greater concern than type 1 error, as it would lead to clinicians ignoring the potential of harmful consequences from cannabis use for patients with psychosis. Committing type 1 error (rejecting the null hypothesis although the risk of relapse of psychosis is not different between continued users of cannabis and non-users) seems to be less problematic in this context, as it would not necessarily have an adverse impact on illness course of psychosis patients using cannabis.

Second, when evaluating the effect of different types of cannabis (skunk-type vs. hash-type), few subjects (n=8) in the continued hash(resin)-user group may have undermined our ability to detect harm related to ongoing hash use. Nevertheless, a similar finding was also reported in a case-control study, which did not find an increased risk of onset of psychosis linked to the use of hash-type cannabis (Di Forti,

Marconi, et al., 2015). Finally, I was unable to separately investigate those who started using cannabis following the onset of psychosis but had no history of premorbid regular use due to a lack of power, as only two subjects (1.3%) fell into this category.

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8 APPENDICES

8.1 APPENDIX I: PUBLICATIONS

Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis

Tabea Schoeler, Anna Monk, Musa B Sami, Ewa Klamerus, Enrico Foglia, Ruth Brown, Giulia Camuri, A Carlo Altamura, Robin Murray, Sagnik Bhattacharyya

Summary

Background Although the link between cannabis use and development of psychosis is well established, less is known about the effect of continued versus discontinued cannabis use after the onset of psychosis. We aimed to summarise available evidence focusing on the relationship between continued and discontinued cannabis use after onset of psychosis and its relapse.

Methods In this systematic review and meta-analysis, we searched MEDLINE for articles published in any language from the database inception date up until April 21, 2015 that included a sample of patients with a pre-existing psychotic disorder with a follow-up duration of at least 6 months. We used a combination of search terms for describing cannabis, the outcome of interest (relapse of psychosis), and the study population. We excluded studies if continued cannabis use or discontinued cannabis use could not be established. We compared relapse outcomes between those who continued (CC) or discontinued (DC) cannabis use or were non-users (NC). We used summary data (individual patient data were not sought out) to estimate Cohen's d, which was entered into random effects models (REM) to compare CC with NC, CC with DC, and DC with NC. Meta-regression and sensitivity analyses were used to address the issue of heterogeneity.

Findings Of 1903 citations identified, 24 studies (16 565 participants) met the inclusion criteria. Independent of the stage of illness, continued cannabis users had a greater increase in relapse of psychosis than did both non-users (d_{CC-NC}=0·36, 95% CI 0·22–0·50, p<0·0001) and discontinued users (d_{CC-DC}=0·28, 0·12–0·44, p=0·0005), as well as longer hospital admissions than non-users (d_{CC-NC}=0·36, 0·13 to 0·58, p=0·02). By contrast, cannabis discontinuation was not associated with relapse (d_{DC-NC}=0·02, –0·12 to 0·15; p=0·82). Meta-regression suggested greater effects of continued cannabis use than discontinued use on relapse (d_{CC-NC}=0·36 *vs* d_{DC-NC}=0·02, p=0·04), positive symptoms (d_{CC-NC}=0·15 *vs* d_{DC-NC}=–0·30, p=0·05) and level of functioning (d_{CC-NC}=0·04 *vs* d_{DC-NC}=–0·49, p=0·008) but not on negative symptoms (d_{CC-NC}=-0·09 *vs* d_{DC-NC}=–0·31, p=0·41).

Interpretation Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospital admissions, and more severe positive symptoms than for individuals who discontinue cannabis use and those who are non-users. These findings point to reductions in cannabis use as a crucial interventional target to improve outcome in patients with psychosis.

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Introduction

Cannabis is the most commonly used illicit drug in patients with an existing psychotic disorder.[1] In some studies, about one of every four patients with psychosis meets the criteria for cannabis dependence,[2,3] with rates of use especially high in young people presenting with their first psychotic episode.[2] These rates are much higher than those of the general population[4] or those of people with other psychiatric diagnoses.[5] Although the association between cannabis use and onset of psychotic disorders is well established,[6,7] suggesting that cannabis use is a component cause of the disorder,[8] its effect on the course of psychosis after onset is less clear. This lack of clarity seems mainly related to limitations of study design such as cross-sectional approach, underpowered samples, and no consideration of potential confounders.[9] Some studies[10–12] implicate cannabis use as a potential risk factor for relapse of psychosis as indexed by readmission to hospital, with some evidence supporting a dose–response association.[13] Other studies report worsening of positive psychotic symptoms[14,15] or less time to symptom re-emergence[16] in cannabis-using patients with psychosis compared with non-users. These findings are in line with experimental pharmacological challenge studies reporting that Δ-9-tetrahydrocannabinol (THC), the main psychoactive constituent in cannabis, can induce transient psychotic experiences in healthy individuals and worsen existing symptoms in patients with pre-existing psychosis.[17–20]

If cannabis use were associated with worse outcomes in individuals with established psychosis, then we would expect that those who continue using cannabis would have far worse outcomes compared with those who stop. However, although some evidence suggests that discontinuation of cannabis use might lead to a reduction in readmission rates[21,22] and improvement in symptomatic

Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis

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PAPER 3 (SCHOELER, PETROS, DI FORTI, PINGAULT, ET AL., 2016)

JAMA Psychiatry | Original Investigation

Association Between Continued Cannabis Use and Risk of Relapse in First-Episode Psychosis
A Quasi-Experimental Investigation Within an Observational Study

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IMPORTANCE Cannabis use after first-episode psychosis is associated with poor outcomes, but the causal nature of this association is unclear.

OBJECTIVE To examine the precise nature of the association between continued cannabis use after the onset of psychosis and risk of relapse of psychosis.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study followed up for at least 2 years after the onset of psychosis 220 patients who presented to psychiatric services in South London, England, from April 12, 2002, to July 26, 2013, with first-episode psychosis. Longitudinal modeling (fixed-effects analysis, cross-lagged path analysis) was used to examine whether the association between changes in cannabis use and risk of relapse over time is the result of shared vulnerability between psychosis and cannabis use, psychosis increasing the risk of cannabis use (reverse causation), or a causal effect of cannabis use on psychosis relapse.

INTERVENTIONS Exposure to cannabis within the first and second years after onset of psychosis.

MAIN OUTCOMES AND MEASURES The main outcome measure was relapse of psychosis, defined as subsequent hospitalization for psychosis. Effect of cannabis use status in the first year (C_{t1}) and second year (C_{t2}) and pattern of cannabis use continuation in the first year and second year were modeled for risk of relapse in the first year (R_{t1}) and risk of relapse in the second year (R_{t2}) after psychosis onset.

RESULTS A total of 220 patients with first-episode psychosis were included in the analysis (mean [SD] age, 28.62 [8.58] years; age range, 18-65 years; 90 women [40.9%] and 130 men [59.1%]). Fixed-effects models that adjusted for time-variant (other illicit drug use, antipsychotic medication adherence) and time-invariant (eg, genetic or premorbid environment) unobserved confounders revealed that there was an increase in the odds of experiencing a relapse of psychosis during periods of cannabis use relative to periods of no use (odds ratio, 1.13; 95% CI, 1.03-1.24). Change in the pattern of continuation significantly increased the risk (odds ratio, 1.07; 95% CI, 1.02-1.13), suggesting a dose-dependent association. Cross-lagged analysis confirmed that this association reflected an effect of cannabis use on subsequent risk of relapse ($C_{t1} \rightarrow R_{t2}$: $\beta = 0.44$, $P = .04$) rather than an effect of relapse on subsequent cannabis use ($R_{t1} \rightarrow C_{t2}$: $\beta = -0.29$, $P = .59$).

CONCLUSIONS AND RELEVANCE These results reveal a dose-dependent association between change in cannabis use and relapse of psychosis that is unlikely to be a result of self-medication or genetic and environmental confounding.

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Supplemental content

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Correlation still does not imply causation

We read with intense interest the meta-analysis by Schoeler and colleagues[1] on continued cannabis use in patients with psychosis. Clearly, this issue is timely and important, and the authors should be commended for attempting to provide empirical evidence to inform public policy. However, our enthusiasm was dampened because the interpretation extends beyond the available data.

It is of utmost importance for us to remember that the meta-analysis was based on correlational studies. Each study points out that causation has not been shown; however, a strong tendency exists to accept cannabis use as a so-called component cause of psychosis, which then leads to the conclusion that it is imperative to reduce cannabis use in patients with or at risk for psychosis. Although we understand this impulse is motivated by a concern for public health, we should not allow the consistency of these correlational findings to substitute for actual evidence of causality.

In 2016, we did a critical review[2] of the scientific literature on cannabis and psychosis and concluded that the literature supports the hypothesis that both psychosis and cannabis use are more likely in individuals with a shared vulnerability to misuse of various substances and increased risk for various mental disorders. In other words, the correlation between cannabis use and psychosis is not specific, either with regard to the chemicals found in cannabis or to psychosis as opposed to other disorders.

Schoeler and colleagues[1] stated that rates of cannabis use in patients with psychosis are "higher than… those of people with other psychiatric diagnoses". To support this statement the authors cited an article by Agosti and colleagues,[3] even though Agosti and colleagues clearly concluded, "Alcohol dependence, antisocial personality disorder, and conduct disorder had the strongest associations with cannabis dependence, followed by anxiety and mood disorders". They did not report any association between cannabis and psychosis, presumably because of the low frequency of psychosis in the participants studied.

In our own review,[2] we included seven studies published in the past 3 years that provided information on the issue of specificity. After reviewing the scientific literature we found evidence that bipolar disorder, anxiety disorder, and mood disorder have all been correlated with cannabis use, and reported that psychosis has been correlated with heavy tobacco smoking, heavy alcohol use, stimulant misuse, and sedative misuse. We found no clear evidence for a causal relation between cannabis and psychosis.[2]

According to our shared vulnerability hypothesis, in a given group of cannabis users who have had psychotic episodes, the individuals with the greatest degree of the shared vulnerability would be the most likely to continue cannabis use rather than to discontinue, and they would be the most likely to have recurring episodes of psychosis and require more hospital treatment. As such, these two outcomes should be correlated, even if neither is a cause of the other.

As to whether a public health benefit can be obtained from efforts to reduce cannabis use in patients with psychosis, two randomised controlled trials,[4,5] published in 2013, comparing treatment as usual with treatment as usual plus motivational interviewing and cognitive behaviour therapy that focused on cannabis use, found no beneficial effect of either intervention on either psychotic symptoms or amount of cannabis use.

Our greatest concern is not that someone might be advised to stop using cannabis. We are concerned that a misunderstanding of the relation between cannabis use and psychotic behaviour leads to an oversimplification of the complex developmental nature of substance use and mental disorders. Furthermore, we propose that future studies that limit their data collection to focus only on cannabis and only on psychosis will do little to enhance our understanding of the complexity of this comorbidity.

We declare no competing interests.

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1 Schoeler T, Monk A, Sami MB, et al. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; **3:** 215–25.
2 Ksir C, Hart CL. Cannabis and psychosis: a critical overview of the relationship. *Curr Psychiatry Rep* 2016; **18:** 12.
3 Agosti V, Nunes E, Levin F. Rates of psychiatric comorbidity among U.S. residents with lifetime cannabis dependence. *Am J Drug Alcohol Abuse* 2002; **28:** 643–52.
4 Hjorthøj CR, Fohlmann A, Larsen A-M, Gluud C, Arendt M, Nordentoft M. Specialized psychosocial treatment plus treatment as usual (TAU) versus TAU for patients with cannabis use disorder and psychosis: the CapOpus randomized trial. *Psychol Med* 2013; **43:** 1499–510.
5 Madigan K, Brennan D, Lawlor E, et al. A multi-center, randomized controlled trial of a group psychological intervention for psychosis with comorbid cannabis dependence over the early course of illness. *Schizophr Res* 2013; **143:** 138–42.

Authors' reply

We thank Charles Ksir and Carl Hart for their interest in our Article.[1] We agree that we cannot draw definite conclusions regarding causality from our meta-analysis of cannabis use continuation versus discontinuation in people already psychotic. This was not our purpose because there are already both prospective and experimental studies implicating cannabis use as "a component cause" for psychotic symptomatology.[2] In this regard we should point out that contrary to the authors' assertion, Agosti and colleagues[3] did in fact find an increased risk (odds ratio 3·49, 95% CI 1·35–9·02) of psychosis in patients dependent on cannabis.

See Online for appendix

Ksir and Hart suggest that the association between continued cannabis use and psychotic relapse is the result of a "shared-vulnerability", presumably genetic. However, two recent GWAS studies suggest that the overlap in genetic vulnerability for psychosis and cannabis use is likely to be only modest (appendix). Furthermore, the association of cannabis use with psychotic symptomatology remained significant when the main effect of genetic predisposition was fully[4,5] or partly factored out (appendix). Dose–response relationships in those studies further oppose a shared-vulnerability hypothesis. Contrary to Ksir and Hart's assertion, shared vulnerability also does not explain why discontinuation of cannabis use might be associated with a reduced severity of symptoms in the same individuals who had more severe symptoms while they were using cannabis.[5] Finally, the notion of cannabis use as a risk factor does not contradict the results from the two randomised controlled trials cited by the authors. Considering that the interventions were not effective in reducing cannabis use in those studies (appendix), no differences in outcome between the two intervention groups would be expected, which was the case. Although we appreciate Ksir and Hart's advice for caution, on the basis of the available evidence, we would argue that it seems unlikely that shared genetic vulnerability fully accounts for the association between continued cannabis use and relapse in psychosis.

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1 Schoeler T, Monk A, Sami MB, et al. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; **3:** 215–25.
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Health for all migrants in Latin America and the Caribbean

Migration is a crucial social determinant of health. As Wickramage and Siriwardhana[1] stated, migration is rapidly reshaping the world. For example, labour migrants are increasingly flowing among low-income and middle-income nations in Asia, Africa, and the Middle East.[1] The same pattern is found in Latin America and the Caribbean, where intraregional migration has deepened socioeconomic inequality in the past few decades.[2]

Latin America and the Caribbean has faced inconsistent human rights and health protection for migrants in the past, just as much as other regions.[3] For example, in Chile, about 70% of immigrants come from other Latin America and the Caribbean countries (representing 2·7% of the total population of Chile), and a third of them are estimated to be undocumented or socioeconomically vulnerable.[4] These migrants tend to work in informal jobs and to live in poor quality, overcrowded buildings. Undocumented migrants have limited access to health care and many of them fear using the health-care system when required.[5] Between 20–60% of their income is remitted to their countries of origin, supporting the basic needs of the family they left behind. Effects on health, particularly mental health, are severe and lasting. "I survive here for them, this is my life sacrifice" (Colombian undocumented woman). Migrants use mental health services in Chile even more than the Chileans, irrespective of socioeconomic status.[5]

Health of all migrants is an urgent matter in Latin America and the Caribbean and elsewhere. Health is largely protected through protection of every aspect of people´s life. Health, as a reflection of social justice, must be explicit in all policies, for local populations and migrants equally so.

We declare no competing interests.

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Challenges to estimating the true global burden of mental disorders

Vigo and colleagues[1] in *The Lancet Psychiatry* identify five reasons why the burden of mental disorders might be underestimated in the Global Burden of Disease (GBD) studies. The issues raised are important and, as members of the team that assembles the mental and substance use disorder GBD estimates, we would make the following comments.

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ORIGINAL ARTICLE

The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis

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Background. Effect of cannabis use on memory function is a contentious issue, with effects being different in healthy individuals and patients with psychosis.

Method. Employing a meta-analytic approach we investigated the effects of cannabis use on memory function in patients with psychosis and healthy individuals, and the effect of diagnosis, memory dimension and moderating factors. A total of 88 studies were identified through a systematic literature search, investigating healthy ($n = 7697$) and psychotic ($n = 3261$) individuals. Standardized mean differences between the cannabis user and non-user groups on memory tasks were estimated using random-effects models and the effect-size statistic Cohen's d. Effects of potential moderating factors were tested using mixed-effects models and subgroup analyses.

Results. We found that cannabis use was associated with significantly ($p \leqslant 0.05$) impaired global ($d = 0.27$) and prospective memory ($d = 0.61$), verbal immediate ($d = 0.40$) and delayed ($d = 0.36$) recall as well as visual recognition ($d = 0.41$) in healthy individuals, but a better global memory ($d = -0.11$), visual immediate recall ($d = -0.73$) and recognition ($d = -0.42$) in patients. Lower depression scores and younger age appeared to attenuate the effects of cannabis on memory. Cannabis-using patients had lower levels of depression and were younger compared with non-using patients, whilst healthy cannabis-users had higher depression scores than age-matched non-users. Longer duration of abstinence from cannabis reduced the effects on memory in healthy and patient users.

Conclusions. These results suggest that cannabis use is associated with a significant domain-specific impairment in memory in healthy individuals but not in cannabis-using patients, suggesting that they may represent a less developmentally impaired subgroup of psychotic patients.

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Key words: Cannabis, memory, meta-analyses, psychosis, Δ-9-tetrahydrocannabinol.

Introduction

Cannabis is one of the most frequently used illicit drugs in the world (UN Office on Drugs and Crime, 2010). Young people are using it at an earlier age (Smith & Flatley, 2011), to the extent that it is replacing cigarette smoking as the most common substance used by them (Moss *et al.* 2013). Based on evidence from observational studies, cannabis use has been linked to a number of effects on cognition and behaviour (Ranganathan & D'Souza, 2006; Solowij & Pesa, 2010), with memory being one of the most robustly replicated cognitive functions which has been reported to be impaired following chronic (non-acute) cannabis use (Grant *et al.* 2003; Fletcher & Honey, 2006; Solowij & Battisti, 2008; Solowij & Pesa, 2010; Schoeler & Bhattacharyya, 2013). Meta-analyses of observational studies comparing cannabis-using subjects with non-using subjects have reported small (Grant *et al.* 2003) to medium-sized effects (Schreiner & Dunn, 2012) of cannabis on verbal memory performance, consistent with evidence that regular cannabis use affects the structure (Matochik *et al.* 2005; Yucel *et al.* 2008) and function (Kanayama *et al.* 2004; Sneider *et al.* 2008) of brain regions involved in memory processing. As discussed by Solowij & Battisti (2008), accumulating evidence suggests that the magnitude and persistence of cognitive impairment associated with cannabis use depends on various parameters such as age of onset (Pope *et al.* 2003; Gruber *et al.* 2012), dose (Bolla *et al.* 2002), frequency (Jager *et al.* 2006; Tait *et al.* 2011), and duration of cannabis use (Meier *et al.* 2012) as well as the period of abstinence from cannabis (Pope

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REVIEW

The effect of cannabis use on memory function: an update

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Abstract: Investigating the effects of cannabis use on memory function appears challenging. While early observational investigations aimed to elucidate the longer-term effects of cannabis use on memory function in humans, findings remained equivocal and pointed to a pattern of interacting factors impacting on the relationship between cannabis use and memory function, rather than a simple direct effect of cannabis. Only recently, a clearer picture of the chronic and acute effects of cannabis use on memory function has emerged once studies have controlled for potential confounding factors and started to investigate the acute effects of delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), the main ingredients in the extract of the cannabis plant in pharmacological challenge experiments. Relatively consistent findings have been reported regarding the acute impairments induced by a single dose of Δ9-THC on verbal and working memory. It is unclear whether they may persist beyond the intoxication state. In the long-term, these impairments seem particularly likely to manifest and may also persist following abstinence if regular and heavy use of cannabis strains high in Δ9-THC is started at an early age. Although still at an early stage, studies that employed advanced neuroimaging techniques have started to model the neural underpinnings of the effects of cannabis use and implicate a network of functional and morphological alterations that may moderate the effects of cannabis on memory function. Future experimental and epidemiological studies that take into consideration individual differences, particularly previous cannabis history and demographic characteristics, but also the precise mixture of the ingredients of the consumed cannabis are necessary to clarify the magnitude and the mechanisms by which cannabis-induced memory impairments occur and to elucidate underlying neurobiological mechanisms.

Keywords: cannabis, THC, CBD, memory, neuroimaging, fMRI

Introduction

Marijuana or Cannabis sativa (*C. sativa*) is the most widely used illicit drug,[1,2] and its use often starts during teenage years.[3] Cannabis contains more than 600 ingredients, including over 60 different cannabinoids,[4] which are now recognized for both their toxic and potential therapeutic effects,[5] and that are mediated through their effects on the endogenous cannabinoid system.[6] Delta-9-tetrahydrocannabinol (commonly known as Δ9-THC) is thought to be the principal psychoactive ingredient present in cannabis that is responsible for the acute and adverse effects of cannabis on various cognitive functions including memory and the induction of psychotic symptoms.[7–15] In contrast, the other major cannabinoid that has attracted attention in recent years, cannabidiol (CBD), does not impair cognition,[16] and may have anxiolytic and antipsychotic effects.[17–20] The potency of cannabis that is available on the street can vary and

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ORIGINAL ARTICLE

Continuity of cannabis use and violent offending over the life course

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Background. Although the association between cannabis use and violence has been reported in the literature, the precise nature of this relationship, especially the directionality of the association, is unclear.

Method. Young males from the Cambridge Study of Delinquent Development ($n = 411$) were followed up between the ages of 8 and 56 years to prospectively investigate the association between cannabis use and violence. A multi-wave (eight assessments, T1–T8) follow-up design was employed that allowed temporal sequencing of the variables of interest and the analysis of violent outcome measures obtained from two sources: (i) criminal records (violent conviction); and (ii) self-reports. A combination of analytic approaches allowing inferences as to the directionality of associations was employed, including multivariate logistic regression analysis, fixed-effects analysis and cross-lagged modelling.

Results. Multivariable logistic regression revealed that compared with never-users, continued exposure to cannabis (use at age 18, 32 and 48 years) was associated with a higher risk of subsequent violent behaviour, as indexed by convictions [odds ratio (OR) 7.1, 95% confidence interval (CI) 2.19–23.59] or self-reports (OR 8.9, 95% CI 2.37–46.21). This effect persisted after controlling for other putative risk factors for violence. In predicting violence, fixed-effects analysis and cross-lagged modelling further indicated that this effect could not be explained by other unobserved time-invariant factors. Furthermore, these analyses uncovered a bi-directional relationship between cannabis use and violence.

Conclusions. Together, these results provide strong indication that cannabis use predicts subsequent violent offending, suggesting a possible causal effect, and provide empirical evidence that may have implications for public policy.

Received 25 March 2015; Revised 14 December 2015; Accepted 15 December 2015

Key words: Cannabis, epidemiology, Δ-9-tetrahydrocannabinol, violence.

Introduction

Cannabis is the most widely used illicit drug in most parts of the world (United Nations Office on Drugs and Crime, 2010), with onset of use often during the developmentally critical period of adolescence and persisting through early adulthood (Patton *et al.* 2007). Among the many potential aversive consequences of cannabis use on cognitive, behavioural and mental health outcomes (Lindsay *et al.* 2005; Bhattacharyya *et al.* 2009, 2012*a*, *b*; Schoeler & Bhattacharyya, 2013, Peters *et al.* 2014; Schoeler *et al.* 2016*a*, *b*), previous research has shown that violent behaviour (Johnson *et al.* 1991; Monshouwer *et al.* 2006; Nabors, 2010; Peters *et al.* 2014) or delinquency and aggression in adolescence (Fergusson *et al.* 2002; Monshouwer *et al.* 2006; Chabrol & Saint-Martin, 2009) may result from cannabis use. Pharmacologically, cannabis may cause impairments in response inhibition resulting in behavioural control in vulnerable individuals that may underlie impulsive, violent behaviour, by altering the normal functioning of its underlying neural substrate, the ventrolateral prefrontal cortex in man (Bhattacharyya *et al.* 2014, 2015). Existing observational evidence in this area, mostly cross-sectional, constrains the possibility of drawing causal inferences. Longitudinal evidence in this regard has been limited as well (Friedman *et al.* 1996; Brook *et al.* 2003, 2014; Pedersen & Skardhamar, 2010), mainly lacking in serial assessments over time

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PAPER 8 (SCHOELER ET AL., UNDER REVIEW)

Developmental sensitivity to cannabis use patterns and risk for Major Depressive Disorder in mid-life: Findings from 40 years of follow-up

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Abstract

Background
Evidence regarding the association between cannabis use and depression remain conflicting, especially as studies have not typically adopted a longitudinal design with a follow-up period that was long enough to adequately cover the risk period for onset of depression or systematically dealt with issues such as reverse causation and confounding.

Method
Males from the Cambridge Study in Delinquent Development (CSDD) (N=285) were assessed 7 times from age 8 to 48 years to prospectively investigate the association between cannabis use and risk of Major Depressive Disorder (MDD). A combination of multiple analyses (logistic regression, Cox regression, fixed-effects analysis) was employed to explore the strength and direction of effect within different developmental stages.

Findings
Multiple regression revealed that early onset cannabis use (before age 18) but not late onset cannabis use (after age 27) was associated with a higher risk and shorter time until a subsequent MDD diagnosis. This effect was present in high-frequency ([Odds Ratio (OR) 8.84, 95% Confidence Interval (CI) 1.32-69.27]; [Hazard Ratio (HR) 7.66, 95%CI 1.83-32.07]) and low-frequency early-onset users ([OR 2.55, 95%CI 1.30-4.99]; [HR 2.22, 95%CI 1.24-3.97]). Effect of increased frequency of cannabis use on increased risk of subsequent MDD was observed only for use during adolescence (age 14-18) but not at later life stages, while controlling for observed and non-unobserved time-invariant factors. Conversely, MDD in adulthood (age 18-32) was linked to a reduction in subsequent cannabis use (age 32-48).

Interpretation
The present findings provide evidence supporting a causal association between frequent cannabis use during adolescence and risk of later life depression.

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PAPER 9 (FOGLIA ET AL., 2017)

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REVIEW ARTICLE

Cannabis use and adherence to antipsychotic medication: a systematic review and meta-analysis

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Background. Substance use may increase the risk of non-adherence to antipsychotics, resulting in negative outcomes in patients with psychosis.

Method. We aimed to quantitatively summarize evidence regarding the effect of cannabis use, the most commonly used illicit drug amongst those with psychosis, on adherence to antipsychotic medication. Studies were identified through a systematic database search. Adopting random-effects models, pooled odds ratios (OR) for risk of non-adherence to antipsychotic medications were calculated comparing: cannabis-users at baseline *v.* non-users at baseline; non users *v.* continued cannabis users at follow-up; non-users *v.* former users at follow-up; former users *v.* current users.

Results. Fifteen observational studies ($n = 3678$) were included. Increased risk of non-adherence was observed for cannabis users compared to non-users (OR 2.46, $n = 3055$). At follow-up, increased risk of non-adherence was observed for current users compared to non-users (OR 5.79, $n = 175$) and former users (OR 5.5, $n = 192$), while there was no difference between former users and non-users (OR 1.12, $n = 187$).

Conclusions. Cannabis use increases the risk of non-adherence and quitting cannabis use may help adherence to antipsychotics. Thus, cannabis use may represent a potential target for intervention to improve medication adherence in those with psychosis.

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Key words: Antipsychotic, cannabis use, medication adherence, psychosis.

Introduction

Antipsychotic medications play an essential role in the treatment of psychosis (Sendt *et al.* 2014), but their effectiveness is often hindered by poor adherence (Keith & Kane, 2003). Reviews report mean non-adherence rates between 27% and 49.5% among patients with psychosis (Cramer & Rosenheck, 1988; Lacro *et al.* 2002; Nosè *et al.* 2003), while they may be up to 63% in first-episode psychosis (FEP) samples (Mojtabai *et al.* 2002; Mutsatsa *et al.* 2003). Non-adherence is associated with negative outcomes such as greater risk of relapse, hospitalization and suicide (Higashi *et al.* 2013). Although predictors of non-adherence have been identified (Sendt *et al.* 2014), they are not always easily amenable to intervention. For instance, illness-related factors such as cognitive deficit or lack of insight (Reed *et al.* 2002; Sharma & Antonova, 2003; Buckley *et al.* 2007) represent a feature rather than a co-morbidity of psychosis (Buckley *et al.* 2007) and may be inextricably and circularly linked to non-adherence. Similarly, reduction of side-effects may enhance adherence (Colom *et al.* 2005), but this may often be reached through a trade-off between the desired level of response and a tolerable level of side-effects to ensure the most optimal adherence in a given individual.

By contrast, one of the most consistently reported risk-factors for non-adherence (Fenton *et al.* 1997; Kampman & Lehtinen, 1999; Green, 2006; Buckley, 2007), which may also potentially be amenable to intervention (Grech *et al.* 2005; Addington & Addington, 2007; Conrod *et al.* 2010), is drug use. Cannabis is the most frequently used illicit drug worldwide (Global Drug Survey, 2014), especially in those with psychosis (Green *et al.* 2005; Addington & Addington, 2007), with prevalence estimates of 16–23% for current and 27–42.1% for lifetime use (Koskinen *et al.* 2010). These may be as high as 10–18% for current and 46.9–66% for lifetime use in FEP patients (Foti *et al.* 2010; Van Dijk *et al.* 2012). Cannabis use is also associated with increased risk of psychosis, increased symptom severity (Moore *et al.* 2007), earlier onset (Large *et al.* 2011) and more relapses and hospitalizations (Zammit *et al.* 2008; Schoeler *et al.*

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8.2 APPENDIX II: STUDY MEASUREMENTS

8.2.1 INFORMATION AND CONSENT FORM

Information and Consent Form (not for data entry)

You have been asked to take part in a study being conducted in the South London and Maudsley NHS Trust. Before you decide whether to enter the study, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information and ask any questions if something is not clear or you wish to know more.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

What are the aims of the study?

In our research project we are interested in identifying what the main risk factors that predispose to psychosis are. In particular, we want to know whether there are any genes that increase the risk of developing a psychotic disorder, either alone or by interacting with environmental factors such as stress, cannabis, and infections. Part of the reason why some people become ill may lay in genetic differences between people, in the same way that we are different in the colour of our eyes, hair etc. To achieve this, we will compare the genetic make-up of people with a diagnosis of psychosis with the make-up of people with similar characteristics but no history of mental health problems.

We also aim to establish whether some genes might influence the course of the illness and response to medication. Some patients experience an improvement of their psychiatric symptoms when they are treated with medications, whereas others do not do so well and/or experience severe side-effects. Therefore we aim to look at how genes can influence individual differences in response to drug treatment so that we may be able to choose better drugs for each person. The type of genetic analysis that we carry out is only for research purposes and does not at present produce clinically relevant results.

Finally, an additional aim of the study is to understand how the social environment may contribute to the onset of illness and the illness experience.

Why are we asking for your help?

You have been invited to take part in this study because of the nature of the symptoms that you appear to have been experiencing. During the course of the study approximately 1000 people who have had symptoms like yours will be asked to take part.

Note that a patient does not have to be involved in the GAP project research and, if they decide not to take part, it will not affect their current or future medical care in any way.

What will we ask of you if you take part in the study?

For this project we will ask from you a small sample of blood, about 20 mL (a few tablespoons full) or cheek swab and saliva samples for metabolic and genetic analysis. We may also use your blood and saliva sample to:

1) Measure the level of hormones and proteins contained in the blood serum and in the saliva.
2) Look at the expression of some genes of interest in the white cells contained in the blood.

A medically trained researcher will take the blood sample using disposable sterile equipment. It will only take few minutes as for any routine blood sample. If you are unable or unwilling to give a blood sample it is also possible to perform genetic analysis from cheek swab samples, a simple procedure that (we can show you the kit and illustrate the procedure) collects dead cells present in your saliva and in your

mouth. From the cheek swab sample we cannot measure level of medication or look at expression of genes, we can only extract a small amount of DNA. Therefore we prefer to ask for a blood sample to guarantee a better quality of our results and make the most out of your generous help.

A researcher will demonstrate how to collect the saliva sample and will provide you with the tubes required. The level of some proteins contained in the saliva can give us an indication of differences in the level of stress experienced by healthy volunteers and people suffering from mental illnesses.

We will also ask for some of your time to collect clinical and socio-demographic information using standardised research instruments: diagnostic interview, symptoms rating scale, socio-demographic interview and neuropsychological tests. We may also ask you to participate in an interview asking about your own perspectives on your social environment and your health condition.

If you have already taken part in other research projects at the Institute of Psychiatry, London that involved some of the assessment we are interested in, we will not ask you to undergo them again but we request your permission to use the existing data.

Some people within the study will be invited to undergo an MRI scan of the head and of another region of the body (the adrenal gland, a small gland above the kidney).They will be presented with separate information and consent forms for this procedure.

The sample collection and the clinical assessment will require approximately 3 hours of your time. Moreover we would like to contact you again for follow up (up to 24 months) to repeat the above assessments to investigate changes over time. We will also reimburse any travel expense related to your participation into the study.

We will also ask for your consent to contact your GP, mother (or father) and a sibling. This is 1) to collect information from your GP records and mother about events that may have occurred very early in your life, such as complications during pregnancy and neonatal infections, 2) to conduct some of the same assessments with your sibling that we have conducted with you, and 3) to ask your sibling similar questions that we have asked you about the environment in which you both grew up and experiences you may have had in childhood. We will only contact your GP and/or relative(s) with your explicit consent and we will not disclose any information we have collected from you to them. If you agree for us to contact your mother (or father) and/or a sibling, we will only proceed to interview them if they provide consent.

What are the risks?

The risks involved are those of ordinary blood tests such as small pain and occasionally a small bruise around the area from where the sample has been taken. There is no risk involved in the collection of saliva.

Is Confidentiality guaranteed?

All personal information about you is regarded as strictly confidential; only researchers belonging to the study team, and not external collaborators, know which sample belongs to whom. All the information about you will be coded; you will not be identifiable in any research outcome.

1) The blood samples first and the DNA samples after extraction will be stored in the Institute of Psychiatry secured laboratory until reporting is complete.
2) The samples will be coded using bar codes (numbers and letters not referring to your name or date of birth) that will be entered on a secure computerized data base.
3) The clinical information collected on the sample will be securely held in the Institute of Psychiatry building.

4) Nothing that you have told us will be mentioned to any relative you might give us permission to contact.

The access to the samples and the related information will be restricted to the researchers involved in the study. In case of commercial collaborations only the coded data will be shared, therefore no researcher external to the study team will ever have access to personal data concerning participants.

Any future work will pursue aims related to the topic of this project and any extension of the project beyond 5 years, will be subject to review by a research ethics committee. You are free to withdraw from this study at any point without giving a reason by contacting the researcher whose details are at bottom of the consent form. Withdrawal will not affect any of the care and treatment you receive.

What are the benefits for you of taking part?

This is a research project, looking at comparing a group of healthy volunteers with people experiencing their first psychotic episode. As mentioned before, this study will not produce individual test results for any of the data collected. Therefore we cannot offer direct benefits for you. We will be able to provide all participants with a general summary of our research, when the project is complete, through a project newsletter. Our research study is also described on the Institute of Psychiatry general website (www.iop.kcl.ac.uk), under the Department of Psychosis Studies section.

Who is funding this project?

This study is funded by the The Maudsley Charitable Fund, the Department of Health, **the Wellcome Trust and the European Union**. Thank you very much for your time and once again please ask for more information on both the project and/or your illness/symptoms if it is still unclear.

Contact details for research team:

Dr Marta Di Forti

Institute of Psychiatry

Tel 020 7848 5352

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CONSENT FORM

If you have come to the decision to enter the study after carefully considering the information provided, please read and sign this form.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

Researcher: Dr Marta Di Forti, Institute of Psychiatry

1)	I have read the information sheet and I have been given a copy. I was given the opportunity to ask questions. **I understand why the research is being done and the risks involved**.	**Yes** ☐	**No** ☐
2)	**I agree to give a sample of blood/cheek swab and saliva samples** for research in the above project. I understand how the sample will be collected, that giving the sample is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical treatment or legal rights being affected. I understand that I will be contacted in the future to repeat part of the assessment.	**Yes** ☐	**No** ☐
3)	**I understand that research using the sample I give will involve genetic analysis** aimed at understanding the role of genes in disease and response to drugs, that the data produced are for research rather than clinical purposes, and that these results will have no implications for me personally.	**Yes** ☐	**No** ☐
4)	**I understand I will not receive any 'test' results from this study**, because the assessment I will undergo, does not produce clinically relevant information but just research data. The project newsletter will describe the general importance of any research results obtained.	**Yes** ☐	**No** ☐
5)	**I give permission for my previous research records to be looked at, and information from them to be analysed in strict confidence by responsible professional staff from the research team**. Researchers external to the study team, collaborating in the project (including commercial collaborations) will only access my coded data.	**Yes** ☐	**No** ☐
6)	**I agree that the samples I have given and the information gathered about me can be examined and stored until reporting is complete at the Institute of Psychiatry.** I understand that future authorised research may be performed by researchers other than those who conducted the first project, including researchers from commercial organisations. To guarantee confidentiality, I agree that researchers external to the study team, including those from commercial collaborators, will only have access to coded data and not to personal details. Any future research will only pursue aims related to the topic of this project, and any extension of the project will be subjected to review by a research ethics committee.	**Yes** ☐	**No** ☐
7)	**I consent to the input of coded data obtained from my blood sample and from the information gathered about me into a computer, to be used for statistical analysis and research.** I understand I have the right to request, via the study co-ordinator, to review data concerning me, and to have such data modified if inaccurate, or deleted.	**Yes** ☐	**No** ☐
8)	**I consent to participate in a digitally-recorded interview** about my own perspectives on my health condition and on my social experiences. I understand that this interview would be recorded to ensure that my own views are adequately represented.	**Yes** ☐	**No** ☐
9)	**I understand I will not benefit financially** if this research leads to the development of a new treatment of medical test but my travel expenses will be reimbursed.	**Yes** ☐	**No** ☐

10) I give permission for my GP records to be looked at. **Yes** ☐ **No** ☐

11) I agree to my mother being approached to participate in this study. **Yes** ☐ **No** ☐

Contact details:

Name …….

Address ……..

…….

Phone Number ……

12) I agree to a sibling being approached to participate in this study. **Yes** ☐ **No** ☐

Contact details:

Name …….

Address ……..

…….

Phone Number ……

……	……..	……
Name of Subject	**Date**	**Signature**
……	……..	……
Name of Researcher	**Date**	**Signature**

Contact details for research team:

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Institute of Psychiatry

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8.2.2 CANNABIS-EXPERIENCE QUESTIONNAIRE (CEQ, MODIFIED VERSION)

1. **Have you ever smoked cannabis?**
   O1 Yes
   O0 No

2. **If yes, how old were you when you first tried cannabis?** _____ years
   Pease rate: Did subject tried cannabis before the onset of illness:
   O1 Yes
   O0 No

   Quantity prior onset
   Total number of joints smoked prior to onset: _____
   Total number of days cannabis used prior to onset: _____

3. **Why did you first try cannabis?** (You can tick more than one box)

	Yes	No
My friends were using it	O	O
My family members were using it	O	O
To feel better (to get relief from either physical or psychological discomfort)	O	O
Other, specify_____	O	O

4. **Have you ever had a period in which you smoked cannabis regularly (i.e. at least once per month)?**
   O1 Yes (period lasted for about _____O weeks O months O years)
   O0 No

5. **If yes, how old were you when you started using cannabis regularly (≥ 1/month)?**
   _____ years
   Pease rate: Did subject use cannabis regularly before the onset of illness:
   O1 Yes
   O0 No

6. **Do you currently smoke cannabis regularly?**
   O1 Yes
   O0 No

   If **yes**, why did you continue using cannabis? (You can tick more than one box)

	Yes	No
I like the effect, it gives me a buzz	O	O
It makes me feel relaxed	O	O
It makes me feel less nervous and anxious	O	O
It makes me feel more sociable	O	O
Other, specify_____	O	O

If **yes**, how many grams of cannabis do you usually buy (for yourself):_____ grams
If **yes**, how many grams of cannabis are on average contained in your primary delivery method (e.g. cones/joints/pipes): _____ grams
If **yes**, how long does this amount of cannabis last for: _____ days
If **yes**, how long does 1/8th of cannabis last you? _____ days

> ***Note:*** *In cases of shared cannabis, divide the weight by the number of people it is shared with!*

If **no**, at what age did you stop using cannabis **regularly**? _____

Please state the reason why you stopped:_____

If past user, did the participant stop using cannabis **regularly (> once per months**) before or after the onset.

O1 Before (stopped_____O weeks O months O years before onset)
O2 After (stopped _____ O weeks O months O years after onset)
O3 Continued use
O4 N/A never regular user since onset

When was the last time that you consumed cannabis:_____ days ago

7. Would you like to stop using cannabis one day?

O1 Yes (If yes, explain: _____)
O0 No

8. Does/did cannabis affect your health in any way?

O1 Yes (If yes, explain: _____)
O0 No

9. Does/did cannabis facilitate social situations?

O1 Yes
O0 No

10. How did/do you mostly use cannabis?

O1 I smoke/smoked it in a joint with tobacco
O2 I smoke/smoked it in a joint without tobacco
O3 I smoke/smoked it using a bong
O4 I eat/ate or drink/drunk it

11. Relapse and cannabis?

Following your first episode, did you have a readmission to hospital/contact with HTT while you were a **regular cannabis** user (i.e. cannabis use at least once per month)?

O1 Yes
O2 No
O3 N/A as not used at all or no regular use after onset

12. Duration of regular cannabis use throughout follow up in percentage

O 1 Continued/started regular cannabis use throughout follow up (use = 100% of the time)
O 2 Infrequent regular cannabis use throughout FU (use = min. 60% of the time)
O 3 Infrequent regular cannabis use throughout FU (use = min. 30% of the time)
O 4 Stopped shortly after onset and remained abstinent from cannabis (use ≤ 10% of the time)
O 5 Never regular user since onset

Cannabis history since onset of illness [prior to onset]

1. **Since onset of illness [now/in the past], how often do/did you use cannabis?**
   - O0 No use
   - O1 Every day
   - O2 More than once a week
   - O3 At least once per month
   - O4 A few times a year
   - O5 Only once or twice

   Quantity of cannabis use (specify the number of joints smoked per occasion, e.g. 1 joint a few times a month)
   - O1 < 1 joint
   - O2 1 joint
   - O3 2 or 3 joints
   - O4 4 or more joints

   Mostly shared
   - O1 Yes
   - O0 No

2. **Since onset of illness [now/in the past], when do/did you mostly use cannabis?**
   - O1 At weekends
   - O2 During the day
   - O3 During the evening
   - O4 During the day and evening

3. **Since onset of illness [now/in the past] , do you/did you mostly use cannabis:**
   - O 1 Socially
   - O 2 On your own
   - O 3 Both

4. **Since onset of illness [now/in the past], how much money per week do/did you usually spend on cannabis?**
   - O 1 less than £2.50
   - O 2 £2.50 - £5
   - O 3 £6 - £10
   - O 4 £11 - £15
   - O 5 £16 - £20
   - O 6 above £20

5. **Since onset of illness [now/in the past], what type of cannabis do/did you mostly use?**
   O1 Hash (cannabis resin/solid)

O2 Imported herbal cannabis
O3 Home grown skunk/Sensimilla
O4 Super skunk
O5 Synthetic cannabis
O6 Other (please state): _____

6. Quantity since onset

Total number of joints smoked since onset: _____
Total number of days cannabis used since onset: _____

Drug Use History
Please give participant prompt sheet and read out following instruction:
"Please have a look at the list I handed to you and indicate which drugs you have used in the past. Also please state how often you use/have used it."

Substance	No 0	Yes, regularly (≥ once/month) 1	Just tried 2
Tobacco			
Alcohol			
MDMA or ecstasy			
Cocaine			
Crack cocaine			
Khat or betel nut			
Heroin			
Morphine			
Codeine			
Opium			
LSD			
Mescaline			
Magic mushrooms			
Salvia			
Valium or diazepam			
Temazepam			
Lorazepam			
Glue			
Poppers			
Petrol			
Laughing gas			
Tuinal			
Legal highs			
Drugs not otherwise specified			

1 Year Follow Up Data

Cannabis between onset and 1 year follow up

Cannabis patterns	O0	No use (or only once/twice)
	O1	Intermitted use
	O2	Continued use (min 100% of time regular use)
Percentage of use	O0	0%
	O1	1%-25%
	O2	26%-50% (at least regular use)
	O3	51%-75%
	O4	76%-100%
Cannabis frequency	O0	No use
	O1	Every day
	O2	More than once a week
	O3	At least once per month
	O4	A few times a year
	O5	Only once or twice
Preferred Cannabis type	O1	Hash-type
	O2	Skunk-type
Number of joints per occasion	O1	< 1 joint
	O2	1 joint
	O3	2 or 3 joints
	O4	4 or more joints

Total number of joints smoked between onset and 1 year follow up: _____

1 to 2 Year Follow Up Data

Cannabis between 1 year follow up and 2 year follow up

Cannabis patterns	O0	No use (or only once/twice)
	O1	Intermitted use
	O2	Continued use (min 100% of time regular use)
Percentage of use	O0	0%
	O1	1%-25%
	O2	26%-50% (at least regular use)
	O3	51%-75%
	O4	76%-100%
Cannabis frequency	O0	No use
	O1	Every day
	O2	More than once a week
	O3	At least once per month
	O4	A few times a year
	O5	Only once or twice
Preferred Cannabis type	O1 Hash-type	
	O2 Skunk-type	
Number of joints per occasion	O1	< 1 joint
	O2	1 joint
	O3	2 or 3 joints
	O4	4 or more joints

Total number of joints smoked between 1 year follow up and 2 year follow up:_____

2 Year Follow Up Data - Summary:

Cannabis between onset and 2 year follow up

Cannabis patterns	O0	No use (or only once/twice)
	O1	Intermitted use
	O2	Continued use (min 100% of time regular use)
Percentage of use	O0	0%
	O1	1%-25%
	O2	26%-50% (at least regular use)
	O3	51%-75%
	O4	76%-100%
Cannabis frequency	O0	No use
	O1	Every day
	O2	More than once a week
	O3	At least once per month
	O4	A few times a year
	O5	Only once or twice
Preferred Cannabis type	O1 Hash-type	
	O2 Skunk-type	
Number of joints per occasion	O1	< 1 joint
	O2	1 joint
	O3	2 or 3 joints
	O4	4 or more joints

Total number of joints smoked between onset and 2 year follow up: _____

Other drug use between onset and 2 year follow up

Cigarette daily	O0 No (<10%) O1 Intermitted (10%-50%) O2 Continued (>50%)
Cigarette weekly	O0 No (<10%) O1 Intermitted (10%-50%) O2 Continued (>50%)
Alcohol daily	O0 No (<1 months daily) O1 Daily (> 1 month daily)
Alcohol weekly	O0 No (<10%) O1 Intermitted (10%-50%) O2 Continued (>50%)
Cocaine	O0 No use O1 Experimental (1-5 times) O2 Regular use (>6 times)
Amphetamines	O0 No use O1 Experimental (1-5 times) O2 Regular use (>6 times)
Hallucinogens	O0 No use O1 Experimental (1-5 times) O2 Regular use (>6 times)
Opioids	O0 No use O1 Experimental (1-5 times) O2 Regular use (>6 times)
Ketamine	O0 No use O1 Experimental (1-5 times) O2 Regular use (>6 times)
Poppers	O0 No use O1 Experimental (1-5 times) O2 Regular use (>6 times)

8.2.3 SERVICE USE AT ONSET: WHO LIFE CHART (MODIFIED VERSION)

Onset of psychosis: ADMISSON to Hospital

Date of Admission ……/……/…….

Date of Discharge ……/……/……..

Ward Type:

O 0 Acute
O 1 Rehabilitation
O 2 Secure/Forensic
O 3 Other, specify:
_____

MHA Status: Section of Mental Health Act used – **ON ADMISSION**

O 1	Section 2	O 6	Section 37
O 2	Section 3	O 7	Section 37/41
O 3	Section 4	O 8	Section 47
O 4	Section 5 (2)	O 9	Section 48
O 5	Section 5 (4)	O 10	Section 136
		O 11	Informal

MHA Status: Section of Mental Health Act used – **ONCE ADMITTED**

O 1	Section 2	O 6	Section 37
O 2	Section 3	O 7	Section 37/41
O 3	Section 4	O 8	Section 47
O 4	Section 5 (2)	O 9	Section 48
O 5	Section 5 (4)	O 10	Section 136
		O 11	Informal

Source of Referral: What was the source of referral resulting in hospital admission?

O 1	Psychiatrist or other mental health professional	O 4	Accident and Emergency
		O 5	Emergency Clinic
O 2	General practitioner	O 6	Police
O 3	Nurse, other health worker or social worker	O 7	Courts/Prison
		O 8	Other, specify:_____

Reason for Admission: What were the main reasons for admission?

a) Attempted suicide or bodily harm O 0 No O 1 Yes
b) Behaviour perceived as potential danger to himself (e.g., talked of killing or harming himself; refusal of food, etc.) O 0 No O 1 Yes
c) Patient committed an assault, or other violent or hazardous act (e.g., setting fire or destroying property) O 0 No O 1 Yes
d) Behaviour perceived by others as threatening or grossly annoying O 0 No O 1 Yes
e) Deterioration in mental health O 0 No O 1 Yes

f) Other reason, specify:_____ O 0 No O 1 Yes

Family Involvement: Were the patient's family or friends involved in seeking help that resulted in hospital admission?

O 0 No O 1 Yes

Police or CJA Involvement: Were the police or any other criminal justice agency involved in bringing about hospital admission?

O 0 No O 1 Yes

Comments (add further relevant details):

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

8.2.4 RELAPSE ASSESSMENT: WHO LIFE CHART (MODIFIED VERSION)

Relapse Questionnaire (RQ) – Relapse No. ____

Have you had a relapse of your illness?

O 1 Yes

Defined as (pick one or both)

O Re-admission to psychiatric hospital
O Contact with home treatment team (HTT)

Type of admission:

O1 Involuntary
O2 Voluntary

Treatment of relapse (pick one or more)

O Drugs (specify: _____)
O Other biological treatment
(specify: _____)
O Psychosocial treatment
(specify: _____)
O Other
(specify: _____)

O 0 No

Relapse No. _____: ADMISSON to Hospital

Date of Admission ……/……/…….

Date of Discharge ……/……/……..

Ward Type:

O 0 Acute
O 1 Rehabilitation
O 2 Secure/Forensic
O 3 Other, specify:
_____

MHA Status: Section of Mental Health Act used – **ON ADMISSION**

O 1	Section 2	O 6	Section 37
O 2	Section 3	O 7	Section 37/41
O 3	Section 4	O 8	Section 47
O 4	Section 5 (2)	O 9	Section 48
O 5	Section 5 (4)	O 10	Section 136
		O 11	Informal

MHA Status: Section of Mental Health Act used – **ONCE ADMITTED**

O 1	Section 2	O 6	Section 37
O 2	Section 3	O 7	Section 37/41
O 3	Section 4	O 8	Section 47
O 4	Section 5 (2)	O 9	Section 48
O 5	Section 5 (4)	O 10	Section 136
		O 11	Informal

Source of Referral: What was the source of referral resulting in hospital admission?

O 1	Psychiatrist or other mental health professional	O 4	Accident and Emergency
		O 5	Emergency Clinic
O 2	General practitioner	O 6	Police
O 3	Nurse, other health worker or social worker	O 7	Courts/Prison
		O 8	Other, specify:_____

Reason for Admission: What were the main reasons for admission?

g) Attempted suicide or bodily harm O 0 No O 1 Yes
h) Behaviour perceived as potential danger to himself (e.g., talked of killing or harming himself; refusal of food, etc.) O 0 No O 1 Yes
i) Patient committed an assault, or other violent or hazardous act (e.g., setting fire or destroying property) O 0 No O 1 Yes
j) Behaviour perceived by others as threatening or grossly annoying O 0 No O 1 Yes
k) Deterioration in mental health O 0 No O 1 Yes
l) Other reason, O 0 No O 1 Yes
specify:_____

Family Involvement: Were the patient's family or friends involved in seeking help that resulted in hospital admission?

O 0 No O 1 Yes

Police or CJA Involvement: Were the police or any other criminal justice agency involved in bringing about hospital admission?

O 0 No O 1 Yes

Comments (add further relevant details):

Relapse Events (RE): Events around RELAPSE No. _____

1. **Where you using cannabis around the time of relapse (i.e. up to 4 weeks before relapse)?** O1Yes O0 No (if **No** - go to question 4)
   O 2 Uncertain (Reason: _____)

   Money per week spent on cannabis?
   O 1 less than £2.50
   O 2 £2.50 - £5
   O 3 £6 - £10
   O 4 £11 - £15
   O 5 £16 - £20
   O 6 Above £20

2. **How often?** **Number of joints** (specify whether per day, week, month etc.)
   O 1 Every day _____
   O 2 More than once a week _____
   O 3 Few time a month _____
   O 4 Few times a year _____
   O 5 Only once or twice _____

3. **What type of cannabis were you using?**
   O1 Hash (cannabis resin/solid)
   O2 Imported herbal cannabis
   O3 Home grown skunk/Sensimilla
   O4 Super skunk
   O 5 Synthetic cannabis
   O 6 Other (please state) _____

4. **Where you using any other drugs around the time of relapse?** O1 Yes O0 No
   (If yes, specify)

			Frequency (for code see frequency table)
Cigarettes/Nicotine	O1 Yes	O0 No	_____
Alcohol	O1 Yes	O0 No	_____
Inhalants	O1 Yes	O0 No	_____
Amphetamines	O1 Yes	O0 No	_____
Crack	O1 Yes	O0 No	_____
Cocaine	O1 Yes	O0 No	_____
Sedatives (not prescribed by doctor)	O1 Yes	O0 No	_____
Opioids (heroin,morphine,methadone)	O1 Yes	O0 No	_____
Hallucinogens	O1 Yes	O0 No	_____

Frequency codes	
1	Every day
2	More than once/week
3	Few times a month
4	Few times a year
5	Only once or twice
6	No use

Ketamine	O1 Yes	O0 No	_____
Others - Specify	O1 Yes	O0 No	_____

Urine drug screen around relapse? O1Yes O0 No

Result: _____

5. **If alcohol every day, how much alcohol (in units as defined in AUDIT) did you use around the time of relapse?**

1 or 2	1 O	10 to 14	5 O
3 or 4	2 O	15 to 19	6 O
5 or 6	3 O	20 to 29	7 O
7 to 9	4 O	30 or more	8 O

6. **Did you stop any of your prescribed medication before the relapse?**

O1 Yes (specify: _____) O0 No
O2 Uncertain (Reason:_____)

How long before did you stop: _____ O days (1) O weeks (2) O months (3)

7. **In your opinion did you experience any life events or difficulty up to 1 month before the relapse**?

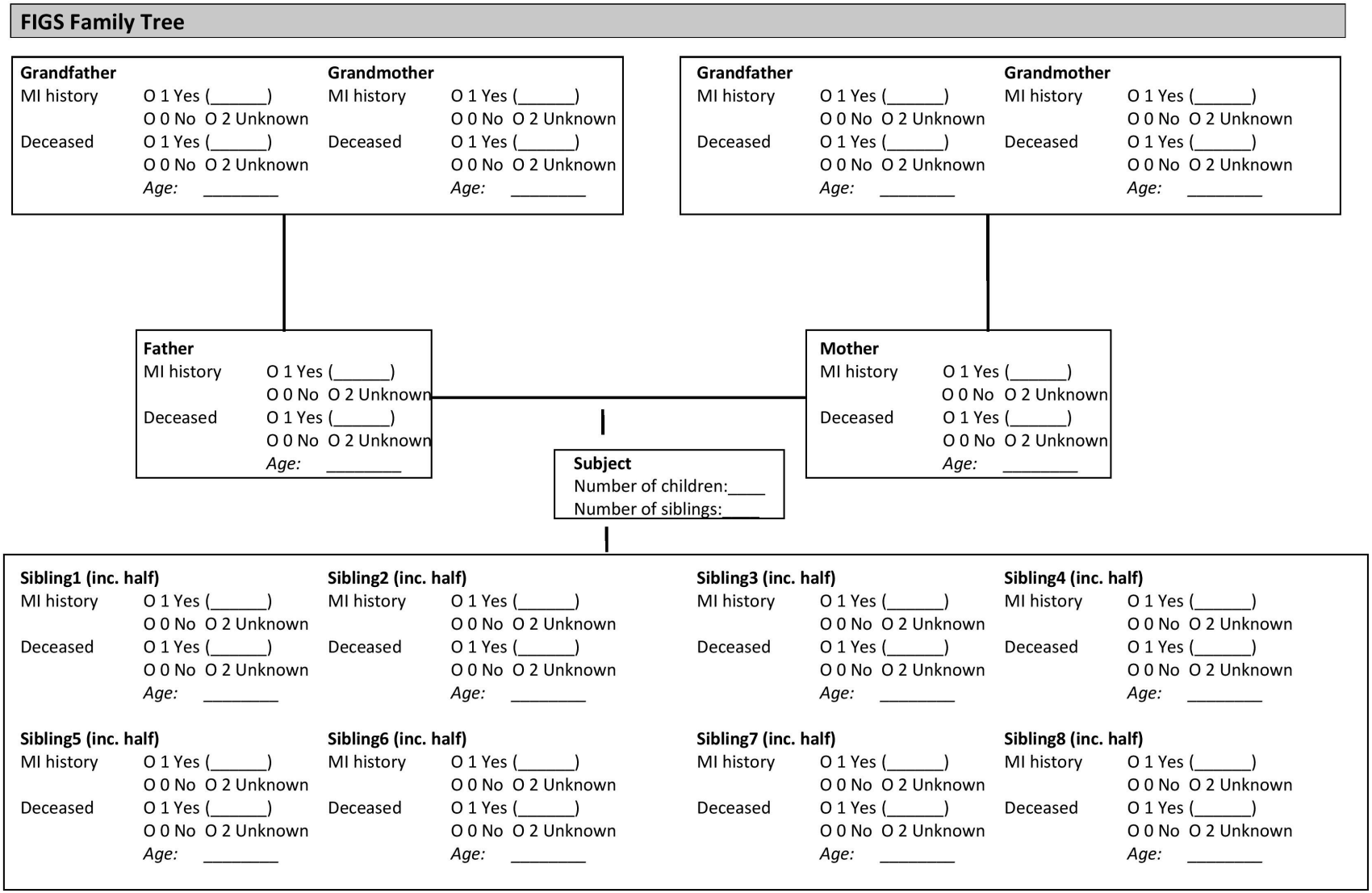
O1 Yes O0 No
If yes, specify: _____

Treatment

1. **Compliance/Attendance between onset and 2 year follow up**
   Rate patient's compliance/attendance at community/follow-up services
   - O 1 Regular compliance/attendance [1-33% missed appointments]
   - O 2 Irregular compliance/attendance [34-66% missed appointments]
   - O 3 None compliance/attendance [67-100% missed appointments]

2. **Reason for Irregular or None Attendance**
   What was the reason(s) why the patient did not fully attend follow-up appointments?

_____
_____
_____


FIGS Family Tree
Grandfather
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Grandmother
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Grandfather
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Grandmother
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Father
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Mother
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Subject
Number of children:____
Number of siblings:____
Sibling1 (inc. half)
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Sibling2 (inc. half)
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Sibling3 (inc. half)
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Sibling4 (inc. half)
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Sibling5 (inc. half)
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Sibling6 (inc. half)
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Sibling7 (inc. half)
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____
Sibling8 (inc. half)
MI history O 1 Yes (_____) O 0 No O 2 Unknown
Deceased O 1 Yes (_____) O 0 No O 2 Unknown
Age: _____

8.3 APPENDIX III: SUPPLEMENTARY MATERIAL

aTable 1. Clinical and functional outcome following onset of FEP

Study	FU	%	N
Symptomatic non-remission			
Greenstein, Wolfe, Gochman, Rapoport, and Gogtay (2008)	0.3	71	56
Üçok et al. (2006)	1	37	74
Haukvik et al. (2016)	1	42	79
Hassan and Taha (2011)	2	49	37
Fraguas et al. (2014)	2	47	80
Gearing et al. (2009)	2	60	87
Pencer et al. (2005)	2	49	69
Wunderink et al. (2009)	2	48	125
D. G. Robinson, Woerner, McMeniman, Mendelowitz, and Bilder (2004)	5	53	118
Henry et al. (2010)	7	59	651
Eggers, Bunk, Volberg, and Röpcke (1999)	42	75	44
L. Clausen et al. (2014)	5	45	314
Faber et al. (2012)	2	48	124
A Malla et al. (2008)	2	23	189
Larsen, Moe, Vibe-Hansen, and Johannessen (2000)	1	44	43
Wunderink, Nieboer, Wiersma, Sytema, and Nienhuis (2013)	7	32	103
D Wade et al. (2006)	1	5	103
Langeveld et al. (2014)	10	45	178
Levy et al. (2012)	1	10	140
Colizzi et al. (2015)	1	55	205
Crumlish et al. (2009)	8	51	67
Wiersma et al. (1998)	3	65	82
Wiersma et al. (1998)	15	73	82
Simonsen et al. (2007)	1	44	301
Schimmelmann et al. (2007)	1.5	42	363
Ho, Andreasen, Flaum, Nopoulos, and Miller (2000)	0.5	62	47
Holthausen et al. (2007)	2	75	103
Prikryl et al. (2012)	4	43	68
T. J. Craig et al. (2000)	2	48	149
Verma et al. (2012)	2	46	1175
Chang et al. (2016)	3	41	539
Non-recovery			
Wunderink et al. (2009)	2	81	125
D. G. Robinson et al. (2004)	5	86	118
Faber et al. (2012)	2	81	124
Wunderink et al. (2013)	7	71	103
Manchanda, Norman, Malla, Harricharan, and Northcott (2005)	2	58	159
Renwick et al. (2015)	1	59	215
Barbeito et al. (2013)	8	72	98
Svedberg, Mesterton, and Cullberg (2001)	5	85	71
Bertelsen et al. (2009)	1	99	265
Bertelsen et al. (2009)	5	82	265
Tarricone et al. (2014)	1	98	163
Faber et al. (2012)	2	81	124
N. Goater et al. (1999)	5	76	79
Verma et al. (2012)	2	71	1175
Chang et al. (2016)	3	83	539
Depressive episode during follow up			
Sönmez et al. (2013)	1	35	198
Jean Addington et al. (2003)	0.3	28	180
Addington, Leriger et al. (2003)	0.5	17	180

Addington, Leriger et al. (2003)	1	14	180
Upthegrove et al. (2010)	1	39	92
Shepherd et al. (1989)	0.01	39	49
Shepherd et al. (1989)	1	29	49
Shepherd et al. (1989)	5	22	49
Non-remission (negative symptoms)			
L. Clausen et al. (2014)	5	58	314
Grech et al. (2005a)	4	56	89
Möller et al. (2002)	15	59	146
Suicide attempt			
J Addington, Williams, Young, and Addington (2004)	1	15	238
J. Robinson et al. (2010)	8	22	282
H Verdoux et al. (2001)	2	11	65
Cotton et al. (2009)	1.5	19	661
Upthegrove et al. (2010)	1	7	92
Nordentoft et al. (2002)	1	11	275
Ayesa-Arriola et al. (2015)	3	11	397
Togay et al. (2015)	5	11	172
Chow et al. (2005)	1	9	94
Verma et al. (2012)	2	42	1175
Unemployed			
Cotton, Lambert et al. (2009)	1.5	46	661
Barbeito et al. (2013)	8	59	98
Schimmelmann et al. (2007)	1.5	44	636
Albert et al. (2011)	5	70	255
Birchwood et al. (1992)	1	75	137
Chow et al. (2005)	1	22	94
Üçok et al. (2006)	1	53	74
Functional non-remission			
Wunderink et al. (2009)	2	74	125
Faber, Smid et al. (2012)	2	74	124
Wunderink, Nieboer et al. (2013)	7	67	103
Svedberg et al. (2001)	5	64	71
Crumlish et al. (2009)	8	72	67
Hodgekins et al. (2015)	0.5	74	764
Hodgekins et al. (2015)	1	76	764
Chang et al. (2016)	1	80	166
Faber, Smid et al. (2012)	2	74	124
Impaired social functioning			
D. G. Robinson et al. (2004)	5	75	118
Henry et al. (2010)	7	69	651
Hodgekins et al. (2015)	0.5	75	764
Hodgekins et al. (2015)	1	71	764
Crumlish et al. (2009)	8	67	67
Continuous course (continuously psychotic)			
Hassan and Taha (2011)	2	24	37
L. Clausen et al. (2014)	5	55	314
Faridi et al. (2012)	1	57	48
Rund et al. (2007)	1	14	111
Rund et al. (2007)	2	13	111
Larsen et al. (2000)	1	26	43
Grech et al. (2005a)	4	44	89
Wiersma et al. (1998)	3	24	82
Simonsen et al. (2007)	1	23	301
Bertelsen et al. (2009)	5	46	265
Thara et al. (1994)	10	7	76
Andreasen et al. (2013)	5	8	202

Bachmann, Bottmer, and Schröder (2007)	1	5	40
Holthausen et al. (2007)	2	7	103
T. J. Craig et al. (2000)	2	34	149
Suicide rate			
Dutta et al. (2011)	13	3	2132
J Addington et al. (2004)	1	3	238
Parker and Hadzi-Pavlovic (1995)	1	2	120
Valevski et al. (2001)	17	4	351
J. Robinson et al. (2010)	8	4	282
Larsen et al. (2000)	1	0	43
Mitter et al. (2013)	2	2	1397
Opjordsmoen et al. (2010)	2	2	217
Wiersma et al. (1998)	2	2	82
Wiersma et al. (1998)	3	6	82
Wiersma et al. (1998)	5	9	82
Wiersma et al. (1998)	15	11	82
Togay et al. (2015)	5	1	172
Thara et al. (1994)	10	7	76
Wunderink et al. (2009)	2	1	257
Poor insight of mental illness			
Ayesa-Arriola et al. (2014)	3	45	224
Schimmelmann et al. (2007)	1.5	17	636
Violent behaviour			
Langeveld et al. (2014)	10	15	178
Tseliou et al. (2015)	1	14	1098
Chow et al. (2005)	1	5	94
Milton et al. (2001)	3	10	168
Non-adherence medication			
Michele Hill et al. (2010)	4	25	106
Levy et al. (2012)	1	44	65
Kamali et al. (2006)	0.5	33	60
Miller et al. (2009)	1	19	112
Martin Lambert et al. (2010)	1.5	66	265
Colizzi et al. (2015)	1	44	205
Coldham et al. (2002)	1	59	200
Barbeito et al. (2013)	8	49	92
Favre et al. (1997)	1	50	59
Coldham et al. (2002)	1	20	186
Svedberg et al. (2001)	1	18	71
Svedberg et al. (2001)	5	33	71
Schimmelmann et al. (2007)	1.5	61	636
Birchwood et al. (1992)	1	29	137
Linszen et al. (1994)	1	19	93
Bachmann et al. (2007)	1	15	40

Note. FU = Number of years of follow up, N = Number of subject included.
[a]defined as convictions for murder, manslaughter, attempted murder and attempted manslaughter

aTable 2. Relapse rates in first episode psychosis

Study	Country	FU	Outcome	%	N
D. Robinson et al. (1999)	US	5	Relapse (CGI rating)	82	118
D. Addington et al. (2010)	Canada	1	Hospitalisation	23	279
D. Addington et al. (2010)	Canada	2	Hospitalisation	32	279
D. Addington et al. (2010)	Canada	3	Hospitalisation	36	279
D. Addington et al. (2010)	Canada	1	Hospitalisation	22	309
D. Addington et al. (2010)	Canada	2	Hospitalisation	30	309
D. Addington et al. (2010)	Canada	3	Hospitalisation	34	309
T. K. J. Craig et al. (2004)	UK	1.5	Hospitalisation	28	144
Craig, Garety et al. (2004)	UK	1.5	Relapse (clinical rating)	24	144
D. E. Addington, Patten, et al. (2013)	Canada	1	Relapse (clinical rating)	23	200
Addington, Patten et al. (2013)	Canada	2	Relapse (clinical rating)	45	200
Nuechterlein et al. (2006)	US	1	Relapse (BPRS rating)	21	77
Hassan and Taha (2011)	Saudi Arabia	2	Relapse (PANSS rating)	41	37
Gearing et al. (2009)	Canada	1	Hospitalisation	33	87
Gearing, Mian et al. (2009)	Canada	2	Hospitalisation	44	87
Whitehorn, Richard, and Kopala (2004)	Canada	1	Hospitalisation	17	434
Parker and Hadzi-Pavlovic (1995)	Australia	1	Hospitalisation	45	118
Valevski et al. (2001)	Israel	17	Hospitalisation	65	351
Jarbin, Gråwe, and Hansson (2000)	Sweden	1	Relapse (rating clinical notes)[a]	53	15
Jarbin, Gråwe et al. (2000)	Sweden	2	Relapse (rating clinical notes)[a]	73	15
Üçok et al. (2006)	Turkey	1	Relapse (BPRS rating)	34	74
Üçok et al. (2006)	Turkey	1	Hospitalisation	12	74
Patel R et al. (2016)	UK	1	Hospitalisation	21	2026
Patel R et al. (2016)	UK	2	Hospitalisation	29	1738
Patel R et al. (2016)	UK	3	Hospitalisation	34	1461
Patel R et al. (2016)	UK	4	Hospitalisation	36	1184
Patel R et al. (2016)	UK	5	Hospitalisation	39	926
Caseiro et al. (2012)	Spain	1	Relapse[b]	21	150
Caseiro, Pérez-Iglesias et al. (2012)	Spain	2	Relapse[b]	41	145
Caseiro, Pérez-Iglesias et al. (2012)	Spain	3	Relapse[b]	65	140
Faber, Smid et al. (2012)	Netherlands	2	Relapse (PANSS rating)	68	124
Faridi et al. (2012)	Canada	1	Relapse (PANSS rating)	51	48
A Malla et al. (2008)	Canada	2	Relapse (SAPS rating)	30	189
Rund et al. (2007)	Norway	1	Relapse (PANSS rating)	18	111
Rund et al. (2007)	Norway	2	Relapse (PANSS rating)	20	111
Larsen et al. (2000)	Norway	1	Relapse (clinical rating)	18	43
Wunderink et al. (2013)	Netherlands	7	Relapse (PANSS rating)	65	103
D Wade et al. (2006)	Australia	1	Hospitalisation	31	103
D Wade et al. (2006)	Australia	1	Relapse (BPRS rating)	36	98
H. Jackson et al. (2008)	Australia	1	Hospitalisation	18	57
Turkington et al. (2009)	Ireland	1	Relapse (PPHS rating)	34	187
Michele Hill et al. (2010)	Ireland	4	Hospitalisation	51	106
Levy et al. (2012)	Canada	1	Relapse (change in medication)	14	65
Levy et al. (2012)	Canada	1	Relapse (SAPS rating)	22	65
Bergé et al. (2016)	Spain	0.2	Relapse[c]	5	133
Bergé, Mané et al. (2016)	Spain	0.5	Relapse[c]	26	105
Bergé, Mané et al. (2016)	Spain	1	Relapse[c]	31	81
Bergé, Mané et al. (2016)	Spain	2	Relapse[c]	43	62

Wiersma et al. (1998)	Netherlands	1	Relapse (LCS)	43	82
Wiersma et al. (1998)	Netherlands	2	Relapse (LCS)	55	82
Wiersma et al. (1998)	Netherlands	3	Relapse (LCS)	63	82
Wiersma et al. (1998)	Netherlands	4	Relapse (LCS)	70	82
Wiersma et al. (1998)	Netherlands	5	Relapse (LCS)	72	82
Simonsen et al. (2007)	Denmark/Norway	1	Relapse (PANSS rating)	26	301
Bertelsen et al. (2009)	Denmark	1	Hospitalisation	23	265
Bertelsen, Jeppesen et al. (2009)	Denmark	2	Hospitalisation	39	265
Kam et al. (2015)	UK	1	Crisis intervention/ Hospitalisation	23	163
Baeza et al. (2009)	Spain	0.5	Hospitalisation	18	101
Chi et al. (2016)	Taiwan	10	Hospitalisation	71	808
Chi, Hsiao et al. (2016)	Taiwan	0.3	Hospitalisation	25	808
Tiihonen et al. (2011)	Finland	3	Hospitalisation	58	2588
Tarricone et al. (2014)	Italy	1	Hospitalisation	36	163
Faber et al. (2012)	Netherlands	2	Relapse (PANSS rating)	68	124
Birchwood et al. (1992)	UK	1	Hospitalisation	34	137
Chow et al. (2005)	China	1	Hospitalisation	10	94
Thara et al. (1994)	India	10	Relapse (PPHS rating)	83	76
Andreasen et al. (2013)	US	5	Relapse (PANSS rating)	78	202
Barrelet et al. (1990)	Switzerland	0.8	Hospitalisation	24	46
E. Y.-H. Chen et al. (2005)	Hong Kong	1	Hospitalisation	21	93
E. Y.-H. Chen et al. (2005)	Hong Kong	2	Hospitalisation	33	93
E. Y.-H. Chen et al. (2005)	Hong Kong	3	Hospitalisation	40	93
Strasser, Schmauss, and Messer (2004)	Germany	1	Hospitalisation	38	75
Holthausen et al. (2007)	Netherlands	2	Relapse (PANSS rating)	42	103
Shepherd et al. (1989)	UK	5	Hospitalisation	55	49
R. J. Drake et al. (2007)	UK	1.5	Hospitalisation	33	257
Drake, Dunn et al. (2007)	UK	1.5	Relapse	51	236
Tohen et al. (2000)	US	0.5	Relapse (BPRS)	20	102
T. J. Craig et al. (2000)	US	2	Hospitalisation	56	149
Singh et al. (2000)	UK	3	Hospitalisation	46	164

Note. FU = Number of years of follow up, N = Number of subject included.

[a] based on ratings from clinical notes: exacerbation of symptoms accompanied by at least 2 weeks of functional impairment

[b] Relapse (BPRS/CGI, hospitalisation, completed suicide) following clinical improvement (assessed with BPRS/CGI)

[c] Hospitalisation or relapse (PANSS rating)

aTable 3. Prevalence rates of cannabis use reported at onset

Study	%	Cannabis definition	N
Lifetime use: Light use			
Seddon et al. (2015)	59	lifetime use (>1) of cannabis	1027
Faber et al. (2012)	65	lifetime use (>1) of cannabis	124
Di Forti, Marconi, et al. (2015)	67	lifetime use (>1) of cannabis	410
Veen et al. (2004)	53	use (>3) at onset	133
Jonsson et al. (2004)	69	history of regular (NS) cannabis use	90
Hinton et al. (2007)	89	lifetime use (>1) of cannabis	130
Barnes et al. (2006)	64	lifetime use (>1) of cannabis	148
I. Harrison et al. (2008a)	63	lifetime use (>1) of cannabis	85
Manrique-Garcia et al. (2014c)	20	lifetime use (>1) of cannabis	357
Faber, Smid et al. (2012)	35	lifetime use (>1) of cannabis	124
Paruk et al. (2016)	56	lifetime use (>1) of cannabis	45
Lifetime use: Heavy use			
Faridi, Joober et al. (2012)	50	presence lifetime CUD	186
Faber, Smid et al. (2012)	19	daily cannabis use for $\geq$ 1 months/lifetime	124
Miller et al. (2009)	44	presence lifetime CUD	112
Grech et al. (2005a)	26	History of (regular/frequent) use	98
Sarrazin, Louppe, Doukhan, and Schürhoff (2015)	21	presence lifetime CUD without comorbid SUD	171
Onset use: Light use			
Seddon, Birchwood et al. (2015)	27	use (>1) in 3 months prior onset	1027
Caseiro et al. (2012)	47	use (>1) at onset	166
Patel R et al. (2016)	46	use (>1) at onset	2026
J. Stone et al. (2014)	41	use (>1) at onset	502
Faber, Smid et al. (2012)	35	use (>1) at onset	124
Barbeito et al. (2013)	52	use (>1) at onset	98
Foti et al. (2010)	10	use (>1) in 1 month prior onset	229
Hinton, Edwards et al. (2007)	55	use (>1) in the months prior onset	130
González-Pinto et al. (2011)	56	use (> slight problem) in 1 year prior onset	92
Ayesa-Arriola et al. (2014)	40	use (>1) at onset	224
I. Harrison et al. (2008a)	32	use (>1) at onset	85
Bergé et al. (2016)	49	use (>1/week) at onset	133
Batalla et al. (2013b)	38	positive UDS at onset	58
Baeza et al. (2009)	29	use (>1) in 1 month prior onset	110
J Boydell et al. (2006)	50	use (>1) in 1 year prior onset	107
Tarricone et al. (2014)	23	use (>2) in 1 month prior onset	163
Bergh et al. (2016)	23	use (>1) in 1 month prior onset	273
Crespo-Facorro et al. (2007)	47	use (>1/week) in 1 year prior onset	172
Paruk et al. (2016)	38	use (>1) in 3 months prior onset	45
Onset use: Heavy use			
B. Schimmelmann et al. (2012)	54	presence CUD at onset	99
Stone, Fisher et al. (2014)	23	presence CUD at onset	502
L. Clausen et al. (2014)	33	monthly use 1 year prior onset	578
Faridi et al. (2012)	33	presence CUD at onset	186
Di Forti, Marconi, et al. (2015)	30	use (daily) at onset	410
Turkington et al. (2009)	21	presence CUD at onset	272
Levy et al. (2012)	14	presence CUD at onset	65
Van Mastrigt et al. (2004)	31	presence CUD at onset	357
Martin Lambert et al. (2010)	44	presence CUD at onset	605
Veen et al. (2004)	10	CUD in 1 year prior onset	133
Hinton et al. (2007)	27	use (daily) in the months prior onset	130
González-Blanch et al. (2015)	52	presence CUD at onset	81

Ruiz-Veguilla et al. (2009)	55	Heavy cannabis use (daily)	92
Faber et al. (2012)	19	Heavy cannabis use (daily for 1 months)	124
Cantwell et al. (1999)	17	presence CUD at onset	168
Wunderink et al. (2009)	24	presence CUD at onset	125
Prior onset use: Cannabis in UHR			
Valmaggia et al. (2014)	74	lifetime use (>1) of cannabis	182
Valmaggia et al. (2014)	20	use (>1) in 1 month prior assessment	182
Auther et al. (2015)	13	presence CUD at first presentation	341

aTable 4. Course of cannabis use following the onset of psychosis

Study	FU	Discontinuer	Continuer	Starter	N
(Seddon et al., 2015)	1	32%	50%	18%	256
J. Stone et al. (2014)	1	63%	37%	-	128
Faridi, Joober et al. (2012)	1	42%	58%	0%	48
B. Schimmelmann et al. (2012)	1.5	55%	42%	3%	53
Faber et al. (2012)	2	44%	56%	-	43
Caseiro et al. (2012)	3	66%	34%	-	78
L. Clausen et al. (2014)	5	59%	26%	15%	70
González-Blanch et al. (2015)	5	50%	48%	2%	52
Miller et al. (2009)	1	33%	63%	4%	112
Grech et al. (2005a)	4	24%	43%	33%	37
Barbeito et al. (2013)	8	49%	51%	-	98
Hinton, Edwards et al. (2007)	0.2	35%	52%	13%	83
I. Harrison et al. (2008a)	1	44%	52%	4%	27
Baeza et al. (2009)	0.5	52%	32%	16%	31

aTable 5. Quality assessment (Paper 1)

	1.	2.	3.	4.	5.	6.	7.	Total score
van der Meer and Velthorst (2015)	1	1	1	1	1	1	1	7
G. E. Sara et al. (2014)	0	0	1	1	0	0	1	3
Koenders et al. (2014)	0	0	1	0	1	1	0	3
Barrowclough et al. (2013)	1	1	1	1	1	0	1	6
van Dijk et al. (2012b)	0	1	1	1	1	1	1	6
San et al. (2013b)	0	1	1	1	0	0	1	4
Faridi et al. (2012)	0	1	1	1	1	1	1	6
Rentzsch et al. (2011)	1	0	1	0	1	0	0	3
González-Pinto et al. (2009)	0	1	1	1	1	1	1	6
Ringen et al. (2010)	0	0	1	0	1	1	0	3
Baeza et al. (2009)	0	1	0	1	1	1	0	4
Rehman and Farooq (2007)	1	0	1	0	1	0	1	4
Jockers-Scherubl et al. (2007)	0	0	0	0	1	1	0	2
D Wade et al. (2006)	0	1	1	1	1	1	1	6
M. Isaac and Holloway (2005)	0	0	1	0	0	0	0	1
Maremmani et al. (2004)	0	0	1	0	0	0	0	1
Sorbara et al. (2003)	0	1	0	1	1	1	1	5
Bersani et al. (2002)	1	0	1	0	1	1	0	4
Salyers and Mueser (2001)	0	1	1	0	0	1	1	4
Caspari (1999)	1	1	1	1	0	0	1	5
Martinez-Arevalo et al. (1994)	1	0	0	1	0	0	1	3
Linszen et al. (1994)	0	1	0	1	1	1	1	5
Peralta and Cuesta (1992)	1	0	0	0	1	1	1	4
Negrete et al. (1986)	1	1	1	1	1	0	0	5

Note. Quality rating scale (adopted and modified from previous meta-analyses (Mullin et al., 2012b)), with 1=higher quality and 0=lower quality

1. Use of patients with non-affective psychosis
2. Use of consecutive presentations
3. A sample of cannabis users of ≥25 people
4. Re-measurement after a period of follow-up rather than a strictly cross-sectional design
5. Use of structured or semi-structured methods for establishing the history of cannabis use
6. Use of structured or semi-structured methods for establishing the diagnosis of psychosis.
7. Quality of relapse assessment [Coded as 1 if comparable follow up duration between cannabis users and non-users AND relapse outcome measures in the specified follow up interval. Quality was also rated as 0 if follow up duration was shorter than 6 months]

aTable 6. Random Effects Models for cannabis groups

Outcomes of interest	**(1) Continued user vs. Non-user**							**(2) Continued user vs. Discontinued user**							**(3) Discontinued user vs. Non-user**							***p*-mod**
	k	**N**	***d***	***p***	***I*²**	***p Q*-test**	***p* -ET**	**k**	**N**	***d***	***p***	***I*²**	***p Q*-test**	***p*-ET**	**k**	**N**	***d***	***p***	***I*²**	***p Q*-test**	***p*-ET**	
Relapse	24	16157	0.36	<0.0001	84%	<0.0001	0.0002	6	676	0.28	0.0005	0%	0.52	0.72	6	904	0.02	0.82	0%	0.76	0.34	0.043
Time spent in hospital	5	803	0.36	0.02	38%	0.14	0.93	0	0	n/a	n/a	n/a	n/a	n/a	0	0	n/a	n/a	n/a	n/a	n/a	n/a
Positive symptoms	10	1224	0.15	0.04	16%	0.21	0.97	2	83	0.26	0.24	0%	0.76	n/a	2	152	-0.30	0.39	71%	0.06	n/a	0.054
Negative symptoms	10	1202	-0.09	0.37	56%	0.02	0.23	2	83	0.41	0.07	0%	0.37	n/a	2	152	-0.31	0.10	0%	0.65	n/a	0.407
Functioning	9	1198	0.04	0.68	41%	0.09	0.74	3	149	0.47	0.23	84%	0.002	0.76	3	220	-0.49	0.002	14%	0.33	0.91	0.0075

Note. *d*= Cohen's *d*; k=number of studies, N=number of subjects; *p* -ET= *p*-value for Egger's Test for publication bias; *p*-mod = *p*-value for meta-regression comparing *d* between (1) and (3); *p (Q* test) = *p*-value for Q-test for heterogeneity.

aTable 7. Balance of covariates of Propensity Score Matched groups

	Never (regular) cannabis user[a] (n=68)		Intermittent cannabis user[a] (n=62)		Continued cannabis user[a] (Hash-like) (n=16)		Continued cannabis user (Skunk-like/low frequency)[a] (n=46)		Continued cannabis user (Skunk-like/high frequency)[a] (n=60)	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Ethnicity (non-white)	1.27 (0.49 – 3.35)	0.63	0.87 (0.31 – 2.42)	0.80	1.00 (0.13 – 7.98)	1.00	1.27 (0.32 – 5.16)	0.73	2.10 (0.72 - 6.43)	0.18
Gender (Female)	1.00 (0.37 – 2.67)	1.00	1.00 (0.34 – 2.93)	1.00	2.33 (0.18 – 58.01)	0.53	0.60 (0.13 – 2.45)	0.48	0.84 (0.25 - 2.71)	0.77
Other illicit drug use	0.48 (0.02 – 5.30)	0.56	1.00 (0.22 – 4.63)	1.00	1.80 (0.21 – 18.29)	0.59	3.05 (0.82 – 13.20)	0.11	2.15 (0.39 - 16.48)	0.40
Cigarette use	0.79 (0.30 – 2.06)	0.63	1.18 (0.38 – 3.66)	0.78	1.00 (0.03 – 28.82)	1.00	2.53 (0.66 – 11.04)	0.19	1.00 (0.33 - 3.05)	1.00
Age of onset	0.99 (0.93 – 1.05)	0.68	1.00 (0.94 – 1.06)	0.94	0.96 (0.76 – 1.17)	0.67	0.97 (0.90 – 1.05)	0.49	0.97 (0.89 - 1.05)	0.48
Alcohol use	1.55 (0.24 – 12.36)	0.64	0.80 (0.21 – 2.99)	0.74	0.43 (0.02 – 5.61)	0.53	1.32 (0.30 – 6.08)	0.71	2.36 (0.65 - 9.85)	0.20
Onset care intensity	0.69 (0.26 – 1.83)	0.46	0.52 (0.19 – 1.42)	0.21	1.80 (0.21 – 18.29)	0.59	0.84 (0.26 – 2.68)	0.77	1.00 (0.36 - 2.77)	1.00
Medication non-adherence	1.12 (0.43 – 2.93)	0.81	1.30 (0.47 – 3.63)	0.61	1.00 (0.13 – 7.98)	1.00	2.53 (0.66 – 11.04)	0.19	1.71 (0.53 - 5.88)	0.37

Note. CI = 95% Confidence Interval; OR = Odds Ratio estimated from logistic regression analysis, with dichotomized dependent variable [0 = Control group: former (regular) cannabis user; 1 = Treatment group]

[a]Treatment group

aTable 8. Cannabis use pattern and relapse outcome: Multiple regression analyses

	Risk of relapse			**Number of relapses**			**Length of relapse**			**Time to relapse**			**Care intensity at follow up**		
Model 1* (N=256)	*OR*[a]	*95% CI*	*p*	*IRR*[b]	*95% CI*	*p*	*b*[c]	*95% CI*	*p*	*b*[c]	*95% CI*	*p*	*OR*[d]	*95% CI*	*p*
Former (regular) user	0.30	0.11-0.82	**0.02**	0.56	0.31-1.04	0.07	-0.61	-1.55-0.31	0.17	0.22	0.04-0.40	**0.02**	0.32	0.12-0.79	**0.01**
Never (regular) user	0.38	0.14-0.99	**0.05**	0.72	0.41-1.25	0.24	-0.61	-1.48-0.22	0.16	0.21	0.04-0.39	**0.02**	0.63	0.27-1.51	0.30
Intermittent user	0.53	0.19-1.49	0.24	0.69	0.38-1.27	0.24	0.17	-0.75-1.08	0.70	0.16	-0.03-0.35	0.11	0.88	0.34-2.22	0.78
Continued user (Hash-like)	0.56	0.10-2.75	0.47	0.64	0.26-1.59	0.34	-0.94	-2.42-0.62	0.21	0.29	0.01-0.58	**0.05**	0.76	0.16-3.33	0.72
Continued user (Skunk-like/low frequency)	0.74	0.23-2.33	0.60	0.63	0.33-1.12	0.17	-0.20	-1.21-0.83	0.68	0.27	0.06-0.48	**0.01**	0.99	0.34-2.82	0.98
Ethnicity (non-white)	2.36	1.23-4.69	**0.01**	1.82	1.16-2.85	**0.01**	0.97	0.35-1.59	**0.002**	-0.12	-0.23-(-0.01)	**0.03**	1.94	1.08-3.54	**0.03**
Gender (Female)	1.42	0.78-2.60	0.26	1.20	0.82-1.74	0.35	-0.27	-0.83-0.30	0.33	-0.04	-0.14-0.06	0.44	1.51	0.88-2.61	0.13
Other illicit drug use	1.79	0.68-4.76	0.24	1.79	1.05-3.04	**0.03**	0.70	-0.17-1.60	0.10	-0.11	-0.28- 0.07	0.23	1.43	0.60-3.41	0.42
Cigarette use	1.49	0.78-2.83	0.23	1.73	1.12-2.67	**0.01**	0.37	-0.17-0.92	0.20	-0.07	-0.18-0.04	0.24	1.66	0.92-3.02	0.09
Age of onset	1.01	0.97-1.04	0.78	1.00	0.97-1.02	0.82	-0.02	-0.05-0.01	0.30	0.00	-0.01-0.00	0.42	0.99	0.96-1.03	0.71
Alcohol use	1.72	0.75-3.94	0.20	1.14	0.69-1.88	0.60	-0.09	-0.85-0.69	0.81	-0.01	-0.15-0.14	0.90	1.96	0.95-4.08	0.07
Onset care intensity	1.37	1.05-1.84	**0.03**	1.32	1.08-1.60	**0.01**	0.59	0.32-0.87	**<0.001**	-0.03	-0.07-0.02	0.22	1.33	1.03-1.73	**0.03**
Model 2** (N=236)	*OR*[a]	*95% CI*	*p*	*IRR*[b]	*95% CI*	*p*	*b*[c]	*95% CI*	*p*	*b*[c]	*95% CI*	*p*	*OR*[d]	*95% CI*	*p*
Former (regular) user	0.37	0.13-0.98	**0.05**	0.57	0.31-1.07	0.08	-0.98	-1.90-(-0.09)	**0.04**	0.2	0.01-0.38	**0.03**	0.34	0.13-0.85	**0.02**
Never (regular) user	0.47	0.19-1.12	0.09	0.65	0.39-1.09	0.11	-0.78	-1.62-0.01	0.06	0.18	0.02-0.35	**0.03**	0.62	0.28-1.37	0.23
Intermittent user	0.58	0.20-1.64	0.31	0.7	0.37-1.34	0.29	-0.2	-1.19-0.79	0.68	0.14	-0.06-0.34	0.16	0.84	0.33-2.17	0.72
Continued user (Hash-like)	0.93	0.18-4.92	0.93	1.00	0.39-2.53	1.00	-0.41	-1.82-1.28	0.60	0.24	-0.06-0.54	0.13	1.13	0.23-5.13	0.88
Continued user (Skunk-like/low frequency)	0.96	0.31-3.00	0.95	0.77	0.4-1.49	0.43	-0.09	-1.11-0.96	0.87	0.23	0.02-0.45	**0.03**	1.10	0.39-3.13	0.85
Medication non-adherence	3.25	1.79-6.09	**<0.001**	2.29	1.46-3.57	**<0.001**	0.57	-0.01-1.15	**0.05**	-0.15	-0.25-(-0.05)	**0.01**	**3**.36	**1**.93-6.00	**<0.001**

Note. Reference group = Continued user (Skunk-like/high frequency)
*Medication non-adherence not included as a covariate
**Only Medication non-adherence included as a covariate
[a] *OR* = Odds Ratio estimates from multiple logistic regression analysis
[b] *IRR* = Incidence Rate Ratio estimated from negative binomial regression
[c] *b* = Coefficient estimate from negative binomial regression
[d] *OR* = Odds Ratio estimates from multiple ordinal regression analysis

aSupplementary 1. Author's rely

The first study[1] showed that a small proportion of cannabis use in the general population was explained by the polygenic risk score for schizophrenia. The second[2] compared GWAS data concerning cannabis use with GWAS data on 5 different psychiatric disorders; they found a very small overlap with depression but none with schizophrenia. Thus, should there be any shared genetic vulnerability between cannabis use and schizophrenia, it could explain only a small proportion of the association between the two. Furthermore, in two independent studies, the association of cannabis use with psychotic symptomatology remained significant when the main effect of genetic predisposition was factored out[3,4]. Fergusson, Horwood (2005)[3] and Foti, Kotov (2010)[4] employed fixed effects models, which apply the principle of co-twin analysis to longitudinal observational data. In co-twin analysis, monozygotic (MZ) twin pairs who are discordant for the risk factor of interest (cannabis use) are compared on the outcome measure (psychosis). Since the pairs share common genes and common environment, these comparisons control for time-invariant sources of confounding (i.e. not time-variant factors such as epigenetics, stressful life events following the onset etc.), even though the common genes and common environmental confounders are not observed[5]. Another study, which controlled for some of the shared genetic contribution (using a sibling design in which 100% of the common environment and 50% of the common genes are controlled for), is also consistent with this evidence[6]. Dose-response relationships in those controlled studies[3,6] further oppose a shared-vulnerability hypothesis. This is in line with the results from RCT's that aimed to reduce cannabis use in psychosis[7,8].

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